# In the United States Court of Federal Claims

**OFFICE OF SPECIAL MASTERS**

Filed: February 15, 2022

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| HELENE QUINTANA, | * | No. 15-1273V |
| Petitioner, | * | Special Master Sanders |
| v. | * | |
| SECRETARY OF HEALTH AND HUMAN SERVICES, | * | Denial of Entitlement; Influenza ("Flu") Vaccine; Uveitis; Peripheral Ulcerative Keratitis ("PUK"); Herpes Simplex Virus ("HSV"); Herpes Keratitis |
| Respondent. | * | |

*Ronald Homer*, Conway, Homer, P.C., Boston, MA, for Petitioner.
*Joseph Lewis*, United States Department of Justice, Washington, DC, for Respondent.

## DECISION ON ENTITLEMENT[1]

On October 28, 2015, Helene Quintana ("Petitioner") filed a petition for compensation pursuant to the National Vaccine Injury Compensation Program.[2] Pet. at 1, ECF No. 1; 42 U.S.C. §§ 300aa-1 to -34 (2012). Petitioner alleges that the influenza ("flu") vaccine she received on November 3, 2012, caused her to suffer from peripheral ulcerative keratitis ("PUK").[3] Pet. at 1. Petitioner further alleges that her flu vaccine caused her to suffer from "uveitis[4] and subsequently herpes keratitis[5] and related sequelae." Pet'r's Br. at 1, ECF No. 88.

[1] This Decision shall be posted on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). In accordance with Vaccine Rule 18(b), a party has 14 days to identify and move to delete medical or other information that satisfies the criteria in § 300aa-12(d)(4)(B). Further, consistent with the rule requirement, a motion for redaction must include a proposed redacted Decision. If, upon review, I agree that the identified material fits within the requirements of that provision, such material will be deleted from public access.

[2] National Childhood Vaccine Injury Act of 1986, Pub L. No. 99-660, 100 Stat. 3755. Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2012).

[3] Peripheral ulcerative keratitis ("PUK") is "a rare type of keratitis with inflammation of the limbal part of the cornea and nearby sclera, which have cellular infiltration, vascular changes, and ulceration that may cause blindness; it may be a complication of rheumatoid arthritis or a bacterial infection but sometimes is idiopathic." *Dorland's Illustrated Medical Dictionary* 1, 979 (32nd ed. 2012) [hereinafter "*Dorland's*"].

[4] Uveitis is "an inflammation of part or all of the uvea, commonly involving the other tunics of the eye (sclera, cornea, and retina)." *Dorland's* at 2014. The uvea is "vascular layer of eyeball: the middle, pigmented, vascular coat of the eye, comprising the choroid, the ciliary body, and the iris[.]" *Id.* at 1990.

[5] Herpes keratitis is "a viral infection of the eye caused by the herpes simplex virus ("HSV"). It is a virus of the genus *Simplexvirus* that is an etiologic agent of herpes simplex and causes predominantly non[-

After carefully analyzing and weighing all the evidence and testimony presented in this case in accordance with the applicable legal standards,[6] I find that Petitioner has failed to provide preponderant evidence that the flu vaccine she received on November 3, 2012, was the cause-in-fact of her PUK, uveitis, or herpes keratitis. Accordingly, Petitioner is not entitled to compensation.

## I. Procedural History

Petitioner filed her petition for compensation on October 28, 2015. Pet. at 1. On November 5, 2015, Petitioner filed her vaccination record and twelve medical records. Pet'r's Exs. 1–13, ECF Nos. 8-1–9-4. Petitioner filed one additional medical record and a statement of completion on December 8, 2015. Pet'r's Ex. 14, ECF Nos. 10-1, 11. On December 16, 2015, Petitioner submitted two affidavits. Pet'r's Exs. 15–16, ECF Nos. 12-1–12-2. Petitioner filed additional medical records and an amended statement of completion on January 7, 2016. Pet'r's Exs. 17–18, ECF Nos. 15-1–15-2, 16.

Respondent filed his Rule 4(c) report on January 26, 2016, recommending that compensation be denied. Resp't's Report, ECF No. 17. A status conference was held on February 23, 2016, to discuss "concern[s] with the timing of onset and a possible alternate cause." Sched. Order, ECF No. 18; *see also* Min. Entry, docketed Feb. 23, 2016. Following the conference, the presiding special master ordered Petitioner to file medical records "relating to Petitioner's herpes diagnosis and treatment[]" and a status report "delineat[ing] next steps and an appropriate timeline." Sched. Order at 1. Petitioner filed a status report on March 15, 2016, advising that "no additional medical records exist regarding herpes treatment or status." ECF No. 19. Petitioner indicated that "an appropriate next step is to file a medical expert report." *Id.*

On July 12, 2016, after several extensions of time, Petitioner filed an expert report from Frederick Fraunfelder, M.D., and supporting medical literature. Pet'r's Exs. 19–20, ECF Nos. 24-1–24-2. Respondent filed his responsive expert report from Hamid Bassiri, M.D., on September 20, 2016, along with supporting medical literature. Resp't's Exs. A–L, ECF Nos. 27-1–27-12.

The parties convened for a status conference on September 29, 2016, at which time the presiding special master discussed the experts' reports. Sched. Order, ECF No. 28; *see also* Min. Entry, docketed Sept. 29, 2016. The presiding special master noted that the experts failed "to address Petitioner's apparent use of Acyclovir . . . [and] that Petitioner's expert ought to address the potential alternative causes identified by Respondent's expert." Sched. Order at 1. The presiding special master ordered Petitioner to file medical records reflecting whether she was

]genital infections. Primary infection usually occurs in early childhood and is often asymptomatic, although gingivostomatitis and pharyngitis may occur. The virus can pass along nerves and remain latent in ganglia, from which it may be reactivated. Called also herpes simplex virus ("HSV") . . . ." *Dorland's* at 979.

[6] While I have reviewed all of the information filed in this case, only those filings and records that are most relevant to the decision will be discussed. *Moriarty v. Sec'y of Health & Hum. Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("[w]e generally presume that a special master considered the relevant record evidence even though he does not explicitly reference such evidence in his decision.") (citation omitted); *see also Paterek v. Sec'y of Health & Hum. Servs.*, 527 F. App'x 875, 884 (Fed. Cir. 2013) ("[f]inding certain information not relevant does not lead to—and likely undermines—the conclusion that it was not considered.").

pursuing a corneal transplant and a status report clarifying her use of Acyclovir. *Id.* The presiding special master further ordered Petitioner to file a supplemental expert report. *Id.*

On October 27, 2016, Petitioner submitted additional medical records and a supplemental affidavit. Pet'r's Exs. 21–26, ECF Nos. 29-1–29-5, 30-1, 31. The same day, Petitioner filed a motion for extension of time to file her remaining outstanding medical records, which was granted. ECF No. 33. Petitioner filed additional medical records on November 21, 2016. Pet'r's Exs. 27–30, ECF Nos. 34-1–34-5. On November 23, 2016, Petitioner filed a motion for extension of time to file her supplemental expert report, which was granted the same day. ECF No. 35. On December 8, 2016, Petitioner filed an additional medical record. Pet'r's Ex. 31, ECF No. 36-2. Petitioner filed her supplemental expert report on January 5, 2017. Pet'r's Ex. 32, ECF No. 37-1.

This case was reassigned to me on January 9, 2017. ECF Nos. 40–41. After several extensions of time, Respondent filed his supplemental expert report on April 25, 2017. Resp't's Ex. M, ECF No. 45-1. I held a status conference with the parties on May 9, 2017. *See* Min. Entry, docketed May 9, 2017. During the status conference, I discussed my main concerns with Petitioner's expert reports, including "a failure to explain the causal mechanism by which an influenza vaccine causes [T]ype IV hypersensitivity and uveitis; and [] a lack of response to alternative causes identified by Respondent . . . ." Sched. Order at 1, ECF No. 46. Following the conference, I ordered Petitioner to file the outstanding medical literature cited in Petitioner's initial expert report and an additional supplemental expert report clarifying her medical theory and addressing the potential alternative causes identified by Respondent's expert. *Id.*

Petitioner filed her outstanding medical literature on May 11, 2017. Pet'r's Exs. 19, Tabs A, C, ECF Nos. 47-1–47-2. On August 9, 2017, Petitioner submitted a supplemental expert report and supporting medical literature. Pet'r's Exs. 33, Tabs A–F, ECF Nos. 49-1–49-7. Respondent filed a responsive supplemental expert report and supporting medical literature on September 15, 2017. Resp't's Exs. N, O, ECF Nos. 52-1–52-2.

On September 29, 2017, the parties communicated via e-mail and agreed to proceed with an entitlement hearing. Informal Comm., docketed Sept. 29, 2017; Order, ECF No. 53. Petitioner filed updated medical records on April 9 and April 23, 2018, and December 11 and 17, 2019. Pet'r's Exs. 34–40, ECF Nos. 54-1–56-1, 67-1, 70-1. This matter was set for an entitlement hearing on March 2, 2020. Non-PDF Order, docketed Sept. 3, 2019. Petitioner filed her pre-hearing brief on December 12, 2019. Pet'r's Br., ECF No. 69. Respondent filed his pre-hearing response brief on January 10, 2020. Resp't's Resp., ECF No. 72. On January 14, 2020, Petitioner filed additional updated medical records. Pet'r's Exs. 41–43, ECF Nos. 74-1–74-3. Petitioner submitted her pre-hearing reply brief and medical literature on February 14, 2020. Pet'r's Reply Br., ECF No. 85; Pet'r's Exs. 44–45, ECF Nos. 79-1, 81, 82. The entitlement hearing was held as scheduled on March 2, 2020. *See* Min. Entry, docketed Mar. 2, 2020.

Following the entitlement hearing, Petitioner filed her opening post-hearing brief on June 10, 2020. Pet'r's Br., ECF No. 88. On July 27, 2020, Respondent filed his post-hearing response brief. Resp't's Resp., ECF No. 90. Petitioner did not submit a post-hearing reply brief. This matter is now ripe for consideration.

## II. Factual Background

### A. Medical Records

Petitioner's pre-vaccination history is rather "unremarkable[,]" and she was "healthy." Pet. at 1; Resp't's Report at 2; Pet'r's Exs. 3, 4, ECF Nos. 8-3–8-4. Petitioner received an influenza vaccine on November 3, 2012. Pet'r's Ex. 1, ECF No. 8-1. She was fifty-five years old at the time of vaccination. Pet. at 1. On November 12, 2012, Petitioner reported to Lilia Alvarez, D.O. Pet'r's Ex. 2 at 1, ECF No. 8-2. Dr. Alvarez wrote that Petitioner "had [a] stye[7] start after [receiving the] flu shot. Progressed to turning red and swollen on [November 5, 2012]." *Id.* Dr. Alvarez also wrote that Petitioner had a "fever [on November 7, 2012 through November 8, 2012], [which] was gone by [November 10, 2012]." *Id.* Dr. Alvarez further wrote that Petitioner "had [another] stye [on November 10, 2012, which became] worse [on November 11, 2012,]" and that Petitioner was suffering from "a mild cold." *Id.* She noted that Petitioner's "nasal nerves on cheeks are tender[.]" *Id.* Petitioner reported that her vision "fe[lt] blurry from discharge[.]" *Id.* An examination revealed yellow mucous and itchiness, along with pain below the eye. *Id.* Dr. Alvarez's examination also revealed a clear cornea.[8] *Id.* Dr. Alvarez assessed Petitioner with bacterial conjunctivitis[9] of the right eye greater than the left, and she prescribed Tobradex,[10] an antibiotic eyedrop. *Id.* at 2.

On November 13, 2012, Petitioner returned to Dr. Alvarez reporting feeling "much better" after doing hot compresses. *Id.* Petitioner reported "some mild discomfort, but fe[lt] better and [was] less swollen[.]" *Id.* Dr. Alvarez's examination revealed a "30% improvement" in Petitioner's right eye, while her left eye was "better." *Id.* Dr. Alvarez directed Petitioner to continue her antibiotic eye drops for three days and then cut back. *Id.*

Petitioner returned to Dr. Alvarez for a follow-up on December 10, 2012. *Id.* at 3. Petitioner reported "some improvement with [prescription,]" and there was "no discharge[]" but still itchiness. *Id.* Dr. Alvarez's examination revealed dry corneas and yellow discharge and she diagnosed Petitioner with a bacterial infection. *Id.* Dr. Alvarez prescribed Petitioner a different antibiotic eye drop. *Id.*

On January 7, 2013, Petitioner presented to ophthalmologist Michael W. Foote, M.D., with complaints of "pain and redness in her right eye[, which she described as a] 7 out of 10 [in] severity." Pet'r's Ex. 5 at 1, ECF No. 8-5. Petitioner reported that this pain began six weeks prior

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[7] A stye or hordeolum is "a localized, purulent, inflammatory staphylococcal infection of one or more sebaceous glands . . . of the eyelids[.]" *Dorland's* at 869, 1789.

[8] A cornea is "the transparent structure forming the anterior part of the fibrous layer of the eyeball. It consists of five layers: (1) the anterior corneal epithelium, continuous with that of the conjunctiva; (2) the anterior limiting layer . . .; (3) the substantia propria, or stroma; (4) the posterior limiting layer . . .; and (5) the endothelium of the anterior chamber." *Dorland's* at 415.

[9] Conjunctivitis is "inflammation of the conjunctiva, generally consisting of conjunctival hyperemia associated with a discharge." *Dorland's* at 405.

[10] Tobradex is the "trademark for combination preparations of tobramycin and dexamethasone." *Dorland's* at 1933. Tobramycin is "effective against a wide range of aerobic gram-negative bacilli and some gram-positive bacteria, having a range of antibacterial activity similar to that of gentamicin; used topically in the treatment of external infections of the eye and its adnexa." *Id*. Dexamethasone is "an anti-inflammatory and administered orally in replacement therapy for adrenocortical insufficiency . . . ." *Id.* at 504.

and "is constant." *Id.* Petitioner denied any trauma. *Id.* Dr. Foote's examination revealed "diffuse papillary changes" and severe redness of the right eye and "minimal papillary changes, mild injection" in her left eye. *Id.* at 2. Dr. Foote's impression was a "marginal corneal ulcer[11] [in Petitioner's] right eye[,]" which Dr. Foote "suspect[ed was of an] infectious etiology." *Id.* He noted that Tobradex and Petitioner's existing treatment "seem[ed] to make it better[.]" *Id.* at 1. Dr. Foote prescribed Vigamox[12] and tobramycin drops[13] and directed Petitioner to follow up the next day. *Id.*

Petitioner returned to Dr. Foote on January 8, 2013. *Id.* at 3. Petitioner complained of "blurry vision, in and around eye pain, [and] redness. [Her] vision is affected both at near and far." *Id.* In addition to medications described above, Petitioner also reported taking Acyclovir, an antiviral for herpes infections.[14] *Id.* Dr. Foote wrote that a "gram stain [of Petitioner's discharge] was negative for organism." *Id.* Dr. Foote considered the possibility that this was PUK, but "suspect[ed it was] more likely infectious." *Id.*

On January 11, 2013, Petitioner returned to Dr. Foote with worsening symptoms, including "redness, tearing, and light sensitivity." *Id.* at 5. Dr. Foote wrote that Petitioner's condition was "presumed to [be] an infectious keratitis but now [he is] suspecting more a peripheral ulcer keratitis[,] which has progress[ed] dispite [sic] topical antibiotic and negative corneal cultures at this point." *Id.* at 6. He directed Petitioner to continue her current medications, except for Acyclovir, and prescribed a Medrol Dosepak[15] and Durezol, a steroidal eye drop. *Id.* at 6, 7.

Petitioner returned to Dr. Foote on January 14, 2013, and reported that her "condition is improving." *Id.* at 9. During this visit, Dr. Foote noted that he "suspect[ed] possible [rheumatoid arthritis ("RA")] vs. other autoimmune process, she has a family [history] of autoimmune disorders . . . ." *Id.* Dr. Foote also ordered numerous tests, including erythrocyte sedimentation rate ("ESR"), C-reactive protein, antinuclear antibody ("ANA"), and RA factor. *Id.* These results returned on January 28, 2013, and showed a positive ANA and HLA-B27 haplotype. *Id.* at 15. The same day, Dr. Foote noted that Petitioner has a sister with possible RA and a son with possible ankylosing spondylitis.[16] *Id.* at 21. He also indicated that Petitioner's corneal ulcer had "slowly" continued to heal. *Id.* at 16.

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[11] A corneal ulcer is also called ulcerative keratitis, which is "keratitis with ulceration of the corneal epithelium[.]" *Dorland's* at 980.

[12] Vigamox is the brand name for moxifloxacin. *Dorland's* at 1184. Moxifloxacin is an eye drop "effective against many . . . bacteria." *Id.*

[13] *See supra* note 10.

[14] Dr. Foote's notes indicate that Petitioner began taking Acyclovir on January 11, 2013. Pet'r's Ex. 5 at 1. However, Dr. Foote noted during Petitioner's January 8, 2013 appointment that she was on Acyclovir then.

[15] A Medrol Dosepak is a prescription of Medrol. Medrol is the "trademark for preparation of methylprednisolone." *Dorland's* at 1120. Methylprednisolone is "a synthetic glucocorticoid [steroid] derived from progesterone, used in replacement therapy for adrenocortical insufficiency and as an anti[-]inflammatory and immunosuppressant in a wide variety of disorders[.]" *Id.* at 1154.

[16] Ankylosing spondylitis is "a chronic multisystem inflammatory disorder associated with presence of the HLA-B27 antigen, and thus one of the group of seronegative spondyloarthropathies; it usually initially affects the sacroiliac joints and often later involves other joints of the axial skeleton and peripheral joints,

On March 4, 2013, Petitioner returned to Dr. Foote at his "request to re-evaluate blurry vision in [her] right eye." *Id.* at 22. During this visit, Petitioner reported "doing much better from [her] last visit . . . ." *Id.* Dr. Foote noted that Petitioner's ulcer "is finally sealed," and he decreased her steroidal and antibiotic eye drops. *Id.*

On May 10, 2013, Petitioner returned to Dr. Foote to complain of a "reaction to Restasis[17] in both [of her] eyes." *Id.* at 28. She described the "severity [as] moderate[,]" and her "vision is not affected." *Id.* Petitioner further described the onset as "sudden" and noted that the symptoms began "[one] week ago." *Id.* Dr. Foote wrote that Petitioner's PUK had returned. *Id.* Petitioner returned to Dr. Foote ten days later, on May 20, 2013. *Id.* at 33. Petitioner stated that her ulcer was "improving," and she "denie[d] redness, pain, light sensitiv[ity], tearing, or itch[iness]." *Id.* She also stated that her vision was "better" and that she was taking Durezol, Vigamox, and "art[ificial] tears." *Id.* Dr. Foote reaffirmed the PUK diagnosis and noted that it was "improving." *Id.*

Petitioner presented to rheumatologist Karen Smith, M.D., on June 5, 2013. Pet'r's Ex. 8 at 12, ECF No. 8-8. Dr. Smith noted that Petitioner was "here after severe ulcerative keratitis after flu shot." *Id.* An examination revealed "on eye red injected eye ulcer at right internal lower quadrant with limbal haze[, but] otherwise" was a normal exam. *Id.* Dr. Smith diagnosed Petitioner with "Reiter's [syndrome][18] most likely[,]" and she prescribed methotrexate[19] and folic acid.[20] *Id.*

The same day, Petitioner presented to internist Branch Craige, M.D., to establish care. Pet'r's Ex. 9 at 2, ECF No. 8-9. Dr. Craige noted that Petitioner was "here to get acquainted, frustrated over a second episode of PUK . . .[,] which she attributes to our dry Southwest or possibly [an] allergy to a vehicle and whatever eyedrops." *Id.* However, an addendum entered on December 1, 2014, states, "[Petitioner] asked us to amend our initial note to reflect the fact that she attribute[s] her PUK to a reaction to [a flu] vaccine." *Id.* He noted that Petitioner had "just begun therapy with Dr. Karen Smith for Reiter [sic] syndrome[.]" *Id.* Under past medical history, Dr. Craige noted that Petitioner's Reiter's syndrome with PUK had an "onset [of] 2012[.]" *Id.* at 3. Upon examination, Dr. Craige wrote that Petitioner's "right eye seem[ed] somewhat inflamed,"

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causing pain and progressive stiffness and restricted range of motion. Extraskeletal manifestations include ocular, pulmonary, cardiovascular, renal, and neurologic complications." *Dorland's* at 1754.

[17] Restasis is the trademark preparation of cyclosporine. *Dorland's* at 1629. Cyclosporine is an immunosuppressant, "produced as a metabolite by the soil fungus *Tolypocladium inflatum Gams;* it acts by inhibiting activation of helper T lymphocytes. Administered orally or intravenously to prevent and treat rejection in organ transplant recipients, to treat severe psoriasis, and as a disease-modifying antirheumatic drug to treat rheumatoid arthritis; also administered topically to the conjunctiva in the treatment of chronic dry eye." *Id.* at 456.

[18] Reiter's syndrome is "the triad of acute aseptic arthritis, nongonococcal urethritis, and conjunctivitis; . . . It usually affects young men and runs a self-limited but relapsing course. Some authorities now consider this symptom complex to be more appropriately classified as reactive arthritis and not distinguished or named separately." *Dorland's* at 1845.

[19] Methotrexate is "a folic acid antagonist that acts by inhibiting synthesis of DNA, RNA, thymidylate and protein . . . It is also used as an anti[-]psoriatic and antiarthritic in the treatment of severe, recalcitrant, disabling psoriasis and severe rheumatoid and psoriatic arthritis." *Dorland's* at 1151.

[20] Folic acid is "1. a water-soluble vitamin of the B complex . . .; 2. a preparation of folic acid administered orally or parenterally in the prophylaxis and treatment of folic acid deficiency states, including megaloblastic anemia." *Dorland's* at 725.

but was otherwise normal. *Id.* His assessment included "Reiter [sic] syndrome, HLA-B27 positive." *Id.*

On June 21, 2013, Petitioner returned to Dr. Foote for a follow-up. Pet'r's Ex. 5 at 45. Dr. Foote noted that "[t]he erosion over [Petitioner's] right eye has significantly improved, though the epithelial is fairly irregular." *Id.* at 46. Five days later, on June 26, 2013, Petitioner presented to Dr. Smith for continued concerns. Pet'r's Ex. 8 at 11. Dr. Smith wrote that "[Petitioner's] ulcers have healed but her eye is redder. . . . She is on her eye drops and has had her contact in place. No problems with the methotrexate." *Id.* Dr. Smith's examination revealed a "red eye[, but] nothing else." *Id.* Dr. Smith assessed Petitioner with keratitis, prescribed her minocycline,[21] and directed her to stop methotrexate due to her then-upcoming trip to Norway. *Id.*

Petitioner returned to Dr. Foote for a follow-up on July 2, 2013. Pet'r's Ex. 5 at 50. Dr. Foote wrote that Petitioner exhibited "decreased redness." *Id.* Dr. Foote wrote that "[t]he [three] abrasions noted previously have turned into one large abrasion[,]" and that Petitioner had begun to take "Pred [F]orte[.][22]" *Id.*

On July 17, 2013, Petitioner presented to Dr. Smith, who wrote that Petitioner had "severe right eye pain [with] no fever[,] chills[,] cough or rash." Pet'r's Ex. 8 at 10. Upon examination, Petitioner exhibited "severe uveitis with hypopyon[23]" but was "well otherwise." *Id.* Dr. Smith's assessment was that Petitioner's condition "needs aggressive control[,]" and she noted that she had spoken to Dr. Foote *Id.* She prescribed Cimzia[24] and a higher dose of methotrexate. *Id.* Dr. Smith also requested "STAT" Remicade.[25] *Id.* She wrote that the "severity and suddenness of [Petitioner's] flare suggests [B]ehcet's" syndrome.[26] *Id.*

Petitioner returned to Dr. Smith on July 26, 2013, for her first dose of Remicade. *Id.* at 7. During this visit, Petitioner reported "moderate pain[.]" *Id.* Dr. Smith's examination revealed that Petitioner's "eye [was] very red [with] no discharge . . . [and] no edema around [her] eye [and] less corneal edema." *Id.* She assessed Petitioner with "hypopyon uveitis" and noted that she would "defer to optho [sic]." *Id.* Dr. Smith indicated that Petitioner was scheduled to see two additional ophthalmologists that day. *Id.*

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[21] Minocycline is "a semisynthetic broad-spectrum antibiotic . . . ." *Dorland's* at 1168.

[22] Pred Forte is the brand name for prednisolone. Prednisolone is "a synthetic glucocorticoid derived from cortisol, administered orally in replacement therapy for adrenocortical insufficiency and as an anti-inflammatory and immunosuppressant in a wide variety of conditions." *Dorland's* at 1508.

[23] Hypopyon is "an accumulation of pus in the anterior chamber of the eye." *Dorland's* at 905.

[24] Cimzia is the trademark preparation of certolizumab pegol. *Dorland's* at 361. Certolizumab pegol is "a tumor necrosis factor blocker used for reduction of signs and symptoms of Crohn disease; administered by subcutaneous injection." *Id.* at 333.

[25] Remicade is the trademark preparation of infliximab. *Dorland's* at 1623. Infliximab is "a chimeric human-murine immunoglobulin that acts as a tumor necrosis factor blocker; administered intravenously in treatment of Crohn disease and rheumatoid arthritis." *Id.* at 937.

[26] Behcet's syndrome is "a variant of neutrophilic dermatosis of unknown etiology, involving the small blood vessels, characterized by recurrent aphthous ulceration of oral and pharyngeal mucous membranes and genitalia, with skin lesions, severe uveitis, retinal vasculitis, optic atrophy, and often involvement of the joints, gastrointestinal system, and central nervous system." *Dorland's* at 1822.

Petitioner presented to ophthalmologist Mario Di Pascuale, M.D., on July 26, 2013. Pet'r's Ex. 10 at 15, ECF No. 9-1. Dr. Di Pascuale wrote that Petitioner "received [the] flu vaccine on November 2, 2012, then contracted conjunctivitis." *Id.* He continued that this "was treated" but "worsened and [Petitioner] was told [she] had [an] ulcer by Dr. Foote and was treated with steroids[, which] helped." *Id.* During this visit, Petitioner complained of pain, photophobia, and light sensitivity in her right eye. *Id.* Dr. Di Pascuale diagnosed Petitioner with PUK and re-prescribed Acyclovir, while discontinuing Vigamox. *Id.*

The same day, Petitioner saw a second ophthalmologist, Ruben Ramirez, M.D. Pet'r's Ex. 6 at 1, ECF No. 8-6. Dr. Ramirez noted that the onset of Petitioner's condition occurred "after [the] flu vaccine." *Id.* Dr. Ramirez assessed Petitioner with "severe vasculitis with associated keratitis[,]" although he was "unclear if [it was] infectious[,]" as the culture was negative. *Id.* at 5. Dr. Ramirez suggested adding systemic steroids to Petitioner's medications. *Id.* On July 30, 2013, Petitioner was formally prescribed oral steroids by Dr. Di Pascuale. *Id.* at 4.

Petitioner took a trip to Norway in August of 2013. Pet'r's Ex. 11 at 1, ECF No. 9-2. On August 23, 2013, Atle Einar Ostern, M.D., wrote a letter documenting the issues Petitioner experienced while in Norway. *Id.* Dr. Ostern wrote that Petitioner "was admitted to the eye Dep[artment] at Oslo University Hospital [on August 8, 2013]." *Id.* She noted that Petitioner's right eye had "corneal edema . . . with a large corneal epithelial defect[,] which was measured vertically 4.2 [mms] and horizontally 6.7 [mms, and] corneal sensibility was almost absent." *Id.* Dr. Ostern noted that all specimen cultures were negative. *Id.* Dr. Ostern wrote that "the condition may be consistent with an (initial) stromal or endothelial herpes keratitis even if all specimens are negative[,] ([Petitioner] feels the pain was diminished after starting [sic] taking Acyclovir)." *Id.* Dr. Ostern also wrote that the "drastically reduced corneal sensibility . . . has lead [sic] to neurotrophic keratopathy[,]" for which Dr. Ostern gave Botox injections into the "eyelid to induce a complete ptosis." *Id.* Petitioner was treated with lubricants, prophylactic antibiotics, and Valacyclovir tablets,[27] which "gradually improved" Petitioner's condition. *Id.* Petitioner's corneal defect had reduced in size (1.8 mms by 2.5 mms) upon discharge. *Id.* Petitioner was discharged with eye gels, ointments, drops, and Valacyclovir, which Dr. Ostern noted "may [need to] be continued . . . for perhaps months." *Id.*

Upon her return to the United States, Petitioner resumed care with Dr. Smith. Pet'r's Ex. 8 at 6. On August 28, 2013, Dr. Smith wrote that Petitioner received treatment in Norway and had been diagnosed with "herpetic keratitis/vasculitis." *Id.* Dr. Smith noted that a biopsy had "+Abs [(antibodies)] in the serum." *Id.* Dr. Smith diagnosed Petitioner with "Reiter's keratitis with herpes as the AG [aggravating] driver." *Id.* Her plan was for Petitioner to "stay on the Valtrex [] for a week then taper off pred[nisone]." *Id.*

The same day, Petitioner also returned to Dr. Di Pascuale. Pet'r's Ex. 10 at 11. Petitioner reported feeling "better" after her treatment in Norway. *Id.* Dr. Di Pascuale recommended continuing her treatment. *Id.* Two days later, on August 30, 2013, Petitioner returned to Dr. Foote.

[27] Valacyclovir hydrochloride tablets are "used as an antiviral agent in the treatment of genital herpes and herpes zoster in immunocompetent adults; administered orally. Following absorption, valacyclovir is converted by intestinal and hepatic metabolism to the active drug acyclovir." *Dorland's* at 2020. The trademark preparation is Valtrex. *Id.* at 2021.

Pet'r's Ex. 5 at 67. Dr. Foote noted that Petitioner was on oral prednisone and Valtrex, but the remainder of her medications had been discontinued. *Id.*

On September 9, 2013, Petitioner reported to Dr. Di Pascuale with complaints of "eye sensitivity and swelling" while she was tapering off prednisone. Pet'r's Ex. 10 at 9. Upon examination, Dr. Di Pascuale noted a corneal ulcer that was "significantly improved." *Id.* Dr. Di Pascuale diagnosed Petitioner with keratitis and increased her prednisone dosage. *Id.*

Petitioner returned to Dr. Smith on October 8, 2013, and reported "some eye pain[,]" so "she is back on her eye drops." Pet'r's Ex. 8 at 5. Dr. Smith noted that Petitioner was on Valtrex and prednisone. *Id.* Dr. Smith's examination revealed a "cloudy right cornea with limbal injection[.]" Dr. Smith diagnosed Petitioner with "Reiters [sic] [syndrome] with herpes keratitis." *Id.*

On December 2, 2013, Petitioner returned to Dr. Foote, who wrote that "[Petitioner's] eye appears fairly quiet today [without] peripheral inflammation." Pet'r's Ex. 5 at 70–71. However, he noted that Petitioner "ha[d] marked corneal vascularization.[28]" *Id.* at 71. Petitioner reported that she had been in Norway in August and "saw an [sic] uveitis specialist there who [diagnosed] her with herpetic keratouveitis[29] and stated her HLA-B27 status caused her to have a severe reaction to [the] herpes virus." *Id.*

Petitioner had another follow-up for the ulcer in her right eye with Dr. Foote on April 15, 2014. *Id.* at 73. Dr. Foote noted that "[t]he severity [of the ulcer] is improving" and "[t]he condition is resolved." *Id.* He wrote that Petitioner's "[v]ision [wa]s affected both at near and far . . . ." *Id.* Dr. Foote indicated that Petitioner "continue[d] to have vascularization . . . [which has] regress[ed] over time." *Id.* He noted that Petitioner "initially presented with peripheral ulcerative keratitis[,] which was ultimately [diagnosed] as herpetic keratouveitis [that was] exacerbated by her HLA-B27 status." *Id.* Regarding Petitioner's cataract, Dr. Foote wrote that her "condition is moderate to severe [and s]he has posterior synechia from previous uveitis episodes." *Id.* Dr. Foote recommended surgical intervention and to continue taking Acyclovir and prednisone. *Id.*

Petitioner followed up with Dr. Di Pascuale two days later, on April 17, 2014. Pet'r's Ex. 7 at 22, ECF No. 8-7. Dr. Di Pascuale noted that Petitioner had 20/20 vision in her right eye. *Id.* at 23. He wrote that Petitioner no longer had a corneal ulcer, but she still had a corneal scar and neovascularization of the cornea. *Id.* at 24. Dr. Di Pascuale diagnosed Petitioner with a corneal

[28] Corneal vascularization is "any formation of new blood vessels" in the cornea. *Dorland's* at 2026.
[29] Herpetic keratouveitis is "1. Keratitis caused by infection with herpes simplex virus, often with dendritic ulceration . . . 2. Keratitis occurring as a complication of herpes zoster ophthalmicus." *Dorland's* at 979.

scar, scleritis,[30] and a cataract.[31] *Id.* He wrote that "cataract surgery will be required at some point." *Id.* at 25.

On May 8, 2014, Petitioner had another follow-up with Dr. Smith, who wrote that Petitioner was "stable and has not had any new problems other than she was in an accident at work and fell hard on her right thigh and is still limping." Pet'r's Ex. 8 at 2. Dr. Smith's examination revealed "some corneal scarring [in Petitioner's] right eye[,] but no signs of activity [of connective tissue disease ("CTD")[32]]." *Id.* Dr. Smith assessed Petitioner with "CTD in remission" and "traumatic injury right thigh." *Id.* Dr. Smith noted that Petitioner's "CTD [was] in remission [for six months]." *Id.*

Petitioner presented to orthopedist Jacob Heydemann, M.D. on May 22, 2014, for right hip pain that she associated with the work-related injury she experienced on March 15, 2014. Pet'r's Ex. 12 at 5–6, ECF No. 9-3. Petitioner explained that while working for ski patrol, she fell on a patch of ice. *Id.* Dr. Heydemann wrote that Petitioner "has a viral keratitis from a flu vaccine that has affected her right eye and [Petitioner] has also been diagnosed with a rheumatoid type pattern, but its only symptom is that it started after the flu vaccine, unrelated to this trauma [i.e., the hip injury]." *Id.* Dr. Heydemann diagnosed Petitioner with joint pain and ordered an MRI, which showed a "small tear of the anterior lip of the labrum." *Id.* at 11. He treated Petitioner's condition accordingly. *Id.* Dr. Heydemann released Petitioner from his care on September 19, 2014, and noted that Petitioner was still in some hip discomfort. *Id.* at 1.

Petitioner returned to Dr. Di Pascuale on October 7, 2014. Pet'r's Ex. 7 at 8. Petitioner complained of "some headaches and . . . vision fluctuating in the right eye." *Id.* at 9. Dr. Di Pascuale's examination showed punctate epithelial erosions of both corneas, a right corneal scar with corneal neovascularization, and bilateral cataracts. *Id.* at 9–10. Dr. Di Pascuale's impression included dry eye syndrome, corneal scar, a flare of scleritis, and cataracts. *Id.* at 10–11. Dr. Di Pascuale increased Petitioner's Acyclovir dosage and steroid eye drops and ordered Petitioner to follow up in six weeks. *Id.* at 11.

On November 6, 2014, Petitioner returned to Dr. Smith for a follow-up. Pet'r's Ex. 8 at 1. Dr. Smith wrote that Petitioner was "generally stable except she has a permanent eye injury." *Id.* Petitioner reported that her eye injury began after receipt of a flu vaccine. *Id.* Dr. Smith noted that "[i]t is immunologically possible that [the flu vaccine] could be the trigger." *Id.* Dr. Smith's examination revealed that Petitioner had a "red hazy right eye [with a] small amount of clear discharge[,]" but "otherwise [had a] normal exam." *Id.* Dr. Smith assessed Petitioner with

[30] Scleritis is "inflammation of the sclera, with dilation of the scleral, episcleral, and bulbar conjunctival vessels. It may be confined to a sector or diffuse, and presents with severe, boring pain, photophobia, tearing, and decreased visual acuity. It is often associated with systemic disease, particularly rheumatoid arthritis." *Dorland's* at 1679.

[31] A cataract is "a partial or complete opacity on or in the lens of the eye or its capsule, especially one impairing vision or causing blindness. Cataracts are classified by their morphology (size, shape, location) or etiology (cause or time of occurrence)." *Dorland's* at 303.

[32] Connective tissue disease is "any disease that affects the parts of the body that connect the structures of the body together . . . [c]onnective tissues are made up of two proteins: collagen and elastin." *Connective Tissue Diseases,* CLEV. CLINIC, https://my.clevelandclinic.org/health/diseases/14803-connective-tissue-diseases (last visited Feb. 1, 2022).

"inflammatory eye disease.[33]" *Id.* Dr. Smith's plan was for Petitioner to "send [Dr. Smith a] timeline and lot number for [her] initial incident with [the flu] vaccine and [Dr. Smith would] then do a letter for [the] vaccine compensation fund[.]" *Id.*

Petitioner returned to Dr. Di Pascuale on December 4, 2014, complaining of "some headaches and . . . plunctuating in the right eye." Pet'r's Ex. 7 at 6. Dr. Di Pascuale assessed Petitioner with corneal dry eye syndrome, stable sclerokeratitis,[34] which he noted could be HSV-related, a corneal scar, and cataracts. *Id.* at 7, 8. Dr. Di Pascuale increased Petitioner's Acyclovir dosage and eye lubricant. *Id.*

On April 23, 2015, Petitioner returned to Dr. Foote, who wrote that Petitioner's corneal ulcer had "essentially resolved." Pet'r's Ex. 5 at 78. Dr. Foote also wrote that Petitioner "ha[d] corneal thinning, which remains stable[, and] she had some calcification as well. In general, there appears to be some overall reduction in the size of the scar and the vascularity is regressing." *Id.* He indicated that Petitioner was to continue her current treatment regimen, which included prednisolone, serum tears, and Acyclovir. *Id.* Dr. Foote noted that "the entire episode began [three] days subsequent to [a] flu vaccination . . . ." *Id.*

Petitioner saw Dr. Di Pascuale several months later, on July 2, 2015, complaining of "blurry vision." Pet'r's Ex. 7 at 29. Dr. Di Pascuale diagnosed Petitioner with sclerokeratitis, HSV-related, which he noted was "stable." *Id.* at 31. He also maintained his diagnoses of corneal dry eye syndrome, a corneal scar, scleritis, and cataracts. *Id.* Dr. Di Pascuale recommended Petitioner continue taking Acyclovir and using eye drops. *Id.*

Petitioner presented to Lookman Lawal, M.D., on April 18, 2016, for complaints of heart murmurs. Pet'r's Ex. 35 at 1–2, ECF No. 54-2. Dr. Lawal noted that Petitioner had a "flu shot reaction [-] eye inflammatory[.]" *Id.* at 1. He indicated that "[s]he had an autoimmune reaction in her right eye after a flu shot [two] years ago." *Id.* at 2.

On May 6, 2016, Petitioner presented to Dr. Smith for a follow-up and reported vision loss, sensitivity to light, wind, and dust. Pet'r's Ex. 30 at 2, ECF No. 34-5. Dr. Smith noted that Petitioner was on Acyclovir. *Id.* On November 4, 2016, Petitioner returned to Dr. Smith and stated that she was doing well throughout the summer but "was given a skin test for [tuberculosis ("TB")] and she has had [the Bacille Calmette-Guerin ("BCG") vaccine for TB] before. She has had an enormous [reaction] and since then her eyes are flaring." *Id.* at 1. Dr. Smith's examination revealed that Petitioner was experiencing "erythema and redness [that were] moderate [in Petitioner's] right eye [and] mild [in her] left eye." *Id.* Dr. Smith wrote a "[n]ote to avoid all things that stimulate dendritic cells[,] which is vaccines and BCG as it activates her eye disease . . . ." *Id.* Dr. Smith continued to monitor Petitioner's condition and directed her to follow up again in four months. *Id.*

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[33] Inflammatory eye disease is an umbrella term for "a range of conditions associated with eye inflammation" including uveitis, keratitis, conjunctivitis, and thyroid eye disease. *Eye Diseases & Conditions: Eye Inflammation and Inflammatory Eye Disease,* PREVENT BLINDNESS, https://preventblindness.org/eye-inflammation/ (last visited Feb. 1, 2022).

[34] Sclerokeratitis is "inflammation of the sclera and of the cornea." *Dorland's* at 1680.

Petitioner traveled to Norway in late 2017, and while there, returned to Dr. Ostern. Pet'r's Ex. 38 at 1A, ECF No. 56-1. Dr. Ostern summarized Petitioner's medical history and noted that "[o]n November 3, 2012, [Petitioner] was given [the flu] vaccine . . . [and three] days later [she developed a] fever . . . [and] conjunctivitis in both eyes . . . [then d]eveloped assumed peripheral ulcerative keratitis." *Id.* Dr. Ostern continued that "the ulcer redeveloped on [Petitioner's] cornea[.]" *Id.* Dr. Ostern explained that as of the last time Petitioner was in Norway, on August 8, 2013, her diagnosis was "[a]ssumed to be residual [h]erpes [k]eratitis with [u]veitis reaction in [her] right eye[.]" *Id.* She noted that Petitioner's "[s]equelae is seen from assumed residual herpes keratitis . . . [and h]erpes keratitis can be set off by stress[.]" *Id.* at 2A. Dr. Ostern wrote that Petitioner had lost a son in 2015. *Id.* She continued that "[i]n connection with [a] TB test . . . with inoculation in October 2016[, Petitioner] got local swelling in arm, but also at the same time strong swelling around the eyes, mostly around [her] right eye with local irritation without wounds[.]" *Id.* Dr. Ostern concluded that Petitioner "seems to react strongly to vaccines, also around the eyes. This is assumed to secondarily set of [her h]erpes [k]eratitis." *Id.* Petitioner has not filed any additional medical records.

**B. Petitioner's Affidavits**

Petitioner submitted three affidavits in support of her petition and did not testify at the entitlement hearing. *See* Pet'r's Exs. 15, 16, 26, ECF Nos. 12-1, 12-2, 30-1. In her first affidavit, Petitioner averred that no civil actions had previously been filed on her behalf for her vaccine-related injury. Pet'r's Ex. 15 at 1.

In her second affidavit, Petitioner explained that prior to receiving her flu shot on November 3, 2012, she "had never had any major health issues . . . [and she] led an active lifestyle, playing competitive tennis . . . coach[ing] . . . r[unning] and lift[ing] weights several times per week." Pet'r's Ex. 16 ¶ 1. Petitioner wrote that her occupations as a paramedic and member of a ski patrol team kept her "physically fit[.]" *Id.* ¶ 2. She noted that as a paramedic, she was "tasked with driving the ambulance, triaging medical situations[,] and transporting patients to hospital destinations." *Id.* She elaborated that as a member of the ski patrol, she "extract[ed] injured skiers from mountainous terrain." *Id.*

Petitioner described the timeline of her post-vaccination condition. Petitioner averred that after receiving the flu shot on November 3, 2012, she "did not notice anything immediately wrong." *Id.* ¶ 3. She wrote that "[s]everal days later, [she] developed a fever and both of [her] eyes became extremely red, itchy[,] and painful . . . [and] a stye had developed on [her] right eye." *Id.* ¶ 4. Petitioner noted that she "thought [it] was just a normal case of conjunctivitis, and [she] waited to see if it got better . . . [but] it did not." *Id.* She explained that "[o]ver the following couple of days," her fever went away but her eyes worsened, in that "[t]he redness was getting more intense," and her eyes produced a discharge. *Id.* Petitioner wrote that in response, she sought treatment with Dr. Alvarez. *Id.* ¶ 5. Petitioner indicated that "the redness in [he] left eye resolved, but [her] right eye continued to bother [her,]" which led to her referral to ophthalmologist Dr. Foote. *Id.*

She wrote that "a few days before Christmas," prior to presenting to Dr. Foote, her right eye was getting "progressively worse . . . [and she] noticed a white spot on the cornea of her right eye." *Id.* Petitioner noted her "failing eyesight" around this time. *Id.* Petitioner described her visit with Dr. Foote on January 7, 2013, and wrote that "he examined [her] eye and told [her she] had

an ulcer on the cornea of [her] right eye." *Id.* ¶ 6. She noted that she maintained treatment with Dr. Foote "[f]or the next several weeks," and that "the ulcer in [her] right eye started to heal slightly, but [her] vision was not back to normal." *Id.* Petitioner expressed that the tests performed by Dr. Foote "did not reveal any specific cause for [her] eye problems, but [he] did tell [her] that [she] was ANA and HLA-B27 positive." *Id.* Petitioner noted that Dr. Foote prescribed Acyclovir during this appointment, but that she "only took the medication for a short time because the virus cultures were negative, and Dr. Foote told [her] not to take it anymore." Pet'r's Ex. 26 ¶ 1. Petitioner averred that prior to this visit, she had never taken Acyclovir and "had never previously sought medical care concerning any type of herpes infection[,]" as she had no prior "signs or symptoms to suggest [she] had a herpes infection." *Id.* ¶ 2.

Petitioner continued that in June of 2013, she presented to Dr. Smith, who "performed more tests and started [her] on methotrexate." Pet'r's Ex. 16 ¶ 8. Petitioner noted that she noticed her eye to be "slightly better[,]" but by July of 2013, "the pain and blurry vision in the right eye increased dramatically." *Id.* Petitioner averred that at that time, she "had recently stopped taking the steroids that were prescribed to [her], and it appeared [her] eye was worsening." *Id.* In response, Petitioner wrote that she returned to Dr. Foote, "who placed an amniotic membrane graft over [her] cornea in an attempt to heal the ulcer and get the swelling and redness to go down." *Id.*

Petitioner wrote that prior to her travels to Norway in August of 2013, her eye "was very bad[.]" *Id.* ¶ 9. She explained that her eye "hurt to even open the refrigerator as any light would cause [her] great pain . . . [e]ven with the atropine drops[.]" *Id.* Petitioner corroborated that while in Norway, she presented to the Eye Clinic at Oslo University Hospital. *Id.* ¶ 10. She noted that the doctors told her "that the ulcer had now grown to over [six] millimeters wide." *Id.* In response, "[t]hey injected [her] eye with Botox to get it to close to protect the ulcer and help it to heal[,] . . . prescribed different medications[,] and stopped the methotrexate." *Id.* Petitioner wrote that "[t]his made [her] eye much more comfortable." *Id.* Petitioner noted that her eye "continued to be stable[]" on oral steroids, antiviral medication, and "large doses of ibuprofen[]" throughout the fall of 2013. *Id.* ¶ 11. She wrote that "[o]nce the ulcer had healed . . . [she] maintained it with 3–4 steroid drops a day[,] as well as constant lubrication[.]" *Id.*

Next, Petitioner described the effect the issues with her right eye have had on her daily life. *Id.* ¶¶ 7, 12–14. Petitioner wrote that in the spring of 2013, she "had to forego a job offer from an ambulance company . . . [, which had] show[n] a lot of interest in hiring [her] because [she] was licensed in both Texas and New Mexico." *Id.* ¶ 7. She averred that she was not able to pursue this opportunity because of her "worsening eye sight [sic] and the inflammation that continued to affect [her] eye [and] hindered [her] ability to drive and would have negatively affected [her] work performance." *Id.* Petitioner stated that in January of 2014, she began taking classes to become a certified EMS instructor, as her "eye issue had taken away [her] ability to actively respond as a paramedic[.]" *Id.* ¶ 12. She continued that during teaching, she noticed that her "eyesight posed a slight problem[]" because her lack of depth perception "made it difficult to show the students how to intubate properly[] or insert an IV." *Id.*

Petitioner continued that her responsibilities as a member of the ski patrol "changed drastically." *Id.* ¶ 7. She noted as a member of the ski patrol, she used to respond to emergencies by skiing in difficult terrain and transporting injured skiers in a sled. *Id.* Petitioner cited an accident, in which she fell in March of 2014 while "bringing an empty toboggan down the

mountain[.]" *Id.* ¶ 13. She wrote that her lack of depth perception "caused [her] to miss some crucial changes in the terrain and [she] suffered a labral tear in [her] right hip[]" as a result. *Id.* Petitioner indicated that "[a]fter [her] eye injury, [she] was relegated to the ski patrol office . . . a more administrative position." *Id.* ¶ 7. She noted that she still continues to work for the ski patrol, but that she "often find[s her]self tentative on the mountain due to certain light conditions or questionable terrain[, as she] cannot distinguish well between shadows and actual moguls or bumps[.]" *Id.* ¶ 14. Petitioner wrote this "significantly impacts" her safety. *Id.*

She also described her then-current eye condition. *Id.* Petitioner explained that her "eye has been stable[,] and the ulcer has healed, but the whole ordeal has left considerable scarring on [her] right cornea . . . [and she] continue[s] to have trouble with depth perception." *Id.* As an example, she wrote that she has problems "parking a car . . . because [she] do[es not] fully trust [her] spatial vision." *Id.* Petitioner noted that she no longer plays tennis "at a high level[]" but instead "just [] for fun, because sometimes [she] cannot even see the tennis ball . . . ." *Id.* She expressed that she "strive[s] to live as normal a life as possible in light of the continued problems with [her] eye." *Id.*

## III. Experts

### A. Expert Review

#### 1. Petitioner's Expert, Frederick W. Fraunfelder, M.D., M.B.A.

Dr. Fraunfelder received his medical degree from Oregon Health Sciences University ("OHSU") in 1994. Pet'r's Ex. 20 at 3. He completed two post-graduate residencies at Providence Medical Center in Portland, Oregon, and Alice Springs Hospital in Australia in 1995 and 1997, respectively. *Id.* Dr. Fraunfelder completed a residency in ophthalmology at the University of Washington Medical Center in Seattle, Washington in 2000. *Id.* He also completed a fellowship in Cornea/External Disease and Refractive Surgery at the Casey Eye Institute at OHSU in 2002. *Id.* The same year, he became board-certified in ophthalmology. *Id.* at 1. He has served as the Chairman and Distinguished Professor of the Cornea/External Disease, Ocular Oncology and Refractive Surgery of the Mason Eye Institute at the University of Missouri since 2014. *Id.* He also serves as the Clinic Medical Director in the Department of Ophthalmology at the same institution. *Id.* Prior to that, Dr. Fraunfelder was the Director/Chief of the Cornea/External Disease/Refractive Surgery Division at the Casey Eye Institute from 2008–2014. *Id.* He became a Professor of Ophthalmology in the same specialty at OHSU in 2011 until 2014. *Id.* Dr. Fraunfelder's curriculum vitae includes over one-hundred and fifty published articles, book chapters, and abstracts of which he is a listed author. *See id.* at 5–17.

During the hearing, Dr. Fraunfelder explained that his clinical practice involves "see[ing] patients . . . and [he is] a cornea external disease eye specialist[, s]o [he] only see[s] people that have diseases on the front of the eye and the front half of the eye." Tr. 12:14–19. Dr. Fraunfelder stated that he treats patients with uveitis "almost daily[,]" as "[u]veitis is a common condition that occurs in the front of the eye[.]" Tr. 12:20–24. He estimated that he has seen "hundreds" of patients with herpes keratitis. Tr. 13:16–23. He made the same estimation in relation to the number of his patients with uveitis as well. Tr. 13:23–25.

Dr. Fraunfelder submitted three expert reports and testified during the hearing. *See* Pet'r's Exs. 19, 32, 33; Tr. 8:20–63:5. Petitioner offered Dr. Fraunfelder as an expert in ophthalmology without objection, and I recognized him as such. Tr. 14:1–6.

**2. Respondent's Expert, Hamid Bassiri, M.D.**

Dr. Bassiri received his medical degree from the University of Pennsylvania in 2004. Resp't's Ex. B at 1. He received his Ph.D. in immunology from the same institution in 2002. *Id.* Dr. Bassiri completed a residency in general pediatrics at the Children's Hospital of Philadelphia in 2007. *Id.* He also completed a fellowship in pediatric infectious diseases at the same institution in 2010. *Id.* Dr. Bassiri has been an attending physician in the Division of Infectious Disease, Department of Pediatrics at the Children's Hospital of Philadelphia since 2011. *Id.* He has served as an Assistant Professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania since 2013. *Id*. He is board-certified in general pediatrics and pediatric infectious diseases. *Id.* Dr. Bassiri has received numerous awards and honors, and he holds memberships in several professional and scientific societies. *Id.* His curriculum vitae lists over thirty publications, including articles, book chapters, and editorials of which he is a listed author. *See id.* at 3–5.

During the hearing, Dr. Bassiri explained that as part of his clinical practice as an attending in pediatric infectious disease, he "see[s] general infections in presumably immune competent hosts, [but] what [he] specialize[s] more highly in are hosts who have compromise to their immunity." Tr. 64:14–20. He elaborated that he "see[s] many patients with cancer, many patients who are immune modulators because they have . . . unknown autoimmune diseases and/or have what we call primary immune deficiencies[.]" Tr. 64:21–25. Dr. Bassiri described his training in immunology and stated that his "initial training was in T cell development and T cell functions. And subsequent to that, [he] maintain[s] a lab that examines T cells and non-T cell populations for use in cancer immunotherapy." Tr. 65:10–14. He noted that he treats children with dysregulated immunity as part of his work on a multidisciplinary committee. Tr. 65:17–21. He testified that in addition to his other responsibilities as the Associate Program Director for the Pediatric Infectious Disease fellowship, he "see[s] patients roughly about [twenty-five] percent of the time . . . [and] regularly give[s] lectures . . . regarding different concepts of infectious diseases as well as concepts in immunology[.]" Tr. 66:5–6, 12–14.

Dr. Bassiri submitted three expert reports and testified at the hearing. *See* Resp't's Exs. A, M, N; Tr. 64:6–135:5. Respondent offered Dr. Bassiri as an expert in immunology and infectious disease without objection, and I recognized him as such. Tr. 66:17–21.

**B. Expert Reports and Testimony**

**1. Petitioner's Expert, Dr. Fraunfelder**

Dr. Fraunfelder submitted three expert reports and testified during the hearing. Pet'r's Exs. 19, 32, 33; Tr. 8–63. Throughout his written and oral testimony, he relied on his specialization in ophthalmology "to point out that [he is] uniquely qualified to form an opinion in this case." Pet'r's Ex. 32 at 1; Tr. 9–14. In his first expert report, Dr. Fraunfelder wrote that "[t]he event speaks for itself[,]" and Petitioner's "flu vaccine administered on November 3, 2012, more likely than not

substantially contributed [to] or caused her eye condition[.]" Pet'r's Ex. 19 at 2. Dr. Fraunfelder described this as a "domino effect" that began with Petitioner's flu vaccine. *Id*. He opined that "it is reasonable to assume that the flu vaccine led to uveitis. The uveitis led to the [herpes] zoster (shingles) keratitis. The zoster keratitis led [to] neurotrophic keratitis. The neurotrophic keratitis led to a permanent corneal scar and the need for a corneal transplant." *Id.* Dr. Fraunfelder explained that this occurred because the flu vaccine caused a Type IV hypersensitivity reaction, which weakened Petitioner's immune status, and allowed an opportunistic infection like herpes to occur. Tr. 43:21–25. He wrote that "but[-]for the November 3, 2012 flu vaccine and subsequent development of uveitis, [Petitioner] would not have suffered from herpes keratitis." Pet'r's Ex. 19 at 2.

First, Dr. Fraunfelder addressed Petitioner's condition and opined that "shingles occurred in her eye." *Id.* He noted that "[i]t [wa]s most likely unrecognized by her initial doctors treating her eye condition[]" on November 12, 2012. *Id.* Dr. Fraunfelder opined that "[i]t was probably never a peripheral ulcerative keratitis or a bacterial conjunctivitis. It was a uveitis, caused by the vaccine." *Id.* Dr. Fraunfelder stated that he based his opinion on Petitioner's symptom presentation recorded in the notes from her November 12, 2012 appointment. Tr. 15:3–25. Petitioner "had a fever on Tuesday [November 6, 2012] through Wednesday [November 7, 2012,] which was gone by Friday [November 9, 2012]. She had a stye on Saturday [November 10, 2012,] which was worse on Friday [November 9, 2012]. And she had a mild cold . . . pain below her eye[,]" blurred vision, and discharge in the right eye. Tr. 15:13–18 (citing Pet'r's Ex. 2 at 1). Dr. Fraunfelder opined that the redness and pain reported during Petitioner's November 12, 2012 examination were symptoms of uveitis. Tr. 19:10–17. He later stated that Petitioner "could have been[]" experiencing symptoms of uveitis during this visit. Tr. 40:11–15. Dr. Fraunfelder indicated that Dr. Alvarez did not perform tests to confirm the diagnosis of uveitis during Petitioner's November 12, 2012 visit. Tr. 19:24–25.

Dr. Fraunfelder stated that "by pure luck," Dr. Alvarez prescribed treatment, including a low-potency steroid, that "would undertreat [uveitis] but would treat it." Tr. 20:15–18. He opined that "undertreating it with the Tobradex probably would have led to a slight improvement but not an all-the-way improvement[,] which is exactly what happened in this instance." Tr. 20:24–25, 21:1–2 (citing Pet'r's Ex. 2 at 2 indicating a 30% improvement on November 13, 2012). He stated that Petitioner's slight improvement following treatment with Tobradex (which undertreats uveitis) is more consistent with Petitioner having uveitis than herpes keratitis during her November 12, 2012 visit. Tr. 21:9–20. He opined that if Petitioner had the latter, her herpes keratitis would have gotten worse with steroids. *See id.*

He then focused on the visit notes from Petitioner's January 7, 2013 appointment with Dr. Foote to opine that Petitioner had uveitis and was developing herpes keratitis at that time. Tr. 16:9–24, 39:5–8; *see also* Pet'r's Ex. 19 at 1. As support, Dr. Fraunfelder stated that Dr. Foote "found some – some things on the exam that were new to what Dr. Alvarez had noted in her exams." Tr. 16:20–22. Dr. Fraunfelder noted that "[o]f significance[,]" Dr. Foote found "cells [] floating in the front of the eye [] that hadn't been noted before." Tr. 16:22, 17:1–2. Dr. Fraunfelder indicated that Dr. Foote also noted "keratic precipitates[]" on the back of Petitioner's cornea, which "are markers of inflammation in the eye[,]" also not previously noted. Tr. 17:7–9. He wrote that "[k]eratic precipitates are deposits of inflammatory cells on the back of the cornea and are a sign of uveitis."

Pet'r's Ex. 19 at 1. Dr. Fraunfelder defined uveitis as "inflammation of any part of the uvea." Tr. 17:23–24. He opined "[i]t is possible and even probable that [Petitioner] may have had uveitis well before these findings[]" even though they were not documented in her medical records. Pet'r's Ex. 19 at 1.

Next, Dr. Fraunfelder explained that the "[f]lu vaccine is not a vaccine with a live virus of herpes zoster, the virus that causes shingles. However, the flu vaccine can be a trigger to cause an immunologic reaction[.]" *Id.* at 2. He continued that "[w]hen a person develops an eye disease . . . they are susceptible to opportunistic infections from viruses that are dormant within [the body]." *Id.* Based on this, Dr. Fraunfelder opined that Petitioner's "flu vaccine let [sic] to an altered immune status and shingles occurred in her eye." *Id.* He maintained that "the sequence of events that took place was that the flu vaccine caused uveitis. This resulted in an altered immune status whereby the zoster virus was able to arise[,] and this led to further damage." Pet'r's Ex. 33 at 2. He wrote that "[z]oster is an opportunistic infection, and it is highly likely it was activated in the setting of the altered immune state brought about by the uveitis." *Id.* By opportunistic, he explained that herpes zoster "takes the opportunity to cause an infection somewhere when you're weak." Tr. 42:21–23. Dr. Fraunfelder stated that Petitioner "had no history of herpes zoster, making it exceedingly unlikely that the convergence of her flu vaccine, uveitis[,] and zoster was due to coincidence alone." Pet'r's Ex. 33 at 2.

Dr. Fraunfelder commented on Petitioner's treating physicians' opinions that her eye condition was caused or triggered by her flu vaccine. Tr. 41:12–16. He noted that Dr. Ostern did not feel that Petitioner had PUK, but rather a herpes keratitis. Tr. 48:4–17. He testified that these opinions are "significant" to him. Tr. 41:15–17. He stated he would have made the same connection if he were her treater. Tr. 41:16–17. However, Dr. Fraunfelder admitted that throughout the course of his career, he has not seen a patient whereby a vaccination caused uveitis, which allowed the herpes keratitis to manifest, as "that's a rare thing." Tr. 42:24–25, 43:1–7. Dr. Fraunfelder then noted that, "if a rare condition occurs to a patient, it is not rare for them." Pet'r's Ex. 32 at 2. He admitted he has, however, seen an infection cause uveitis and then herpes keratitis. Tr. 43:8–10.

He addressed the connection between the flu vaccine and uveitis. Dr. Fraunfelder stated that "there's a general consensus" in the medical community that "vaccine-induced uveitis occurs[.]" Tr. 31:25–25, 32:1. Dr. Fraunfelder relied on an article by Benage,[35] of which he is also listed author, to explain that "all vaccines, albeit rarely[,]" can cause an immunologic reaction, manifesting as uveitis. Pet'r's Ex. 19 at 2; Pet'r's Ex. 19, Tab A at 1, ECF No. 81-1 (noting that "[a]ll of the widely administered vaccines have been reported to cause uveitis."). The authors noted that "[d]uring a 26-year period, a total of 289 cases of vaccine-associated uveitis were reported to three adverse reaction reporting databases. Hepatitis B [("Hep. B")] vaccine . . . appears to be the leading offender." Pet'r's Ex. 19, Tab A at 1. Dr. Fraunfelder stated that "the flu vaccine . . . was the third most common cause for uveitis based on this [] case series." Tr. 26:19–21. Dr. Fraunfelder relied on an article by London et al.,[36] which used the Naranjo criteria[37] in place of a clinical trial,

[35] M. Benage & F.W. Fraunfelder, *Vaccine-Associated Uveitis*, 113:1 MISSOURI MED. 48–52 (2016).
[36] N. London, et al., *Drug-induced uveitis,* 3 J. OPHTHALMIC INFLAMMATION & INFECTION 43–61 (2013).
[37] The Naranjo criteria, or the Adverse Drug Reaction ("ADR") Probability Scale, was "developed to help standardize assessment of causality for all adverse drug reactions[.]" It consists of 10 questions that are

to show that "the influenza vaccination was 'probable' in causation in relation to uveitis." Tr. 31:13–18 (citing Pet'r's Ex. 45 at 13, ECF No. 79-2). The authors identified a score of 7 to ascribe "probable" causation to the flu vaccine and uveitis. Pet'r's Ex. 45 at 13. Dr. Fraunfelder indicated that the Naranjo criteria "take[] into account a temporal relationship between taking the drug . . . positive rechallenge, positive dechallenge . . . take[] into account is there a plausible biological mechanism, . . . [and] are there other drugs or diseases that could have occurred." Tr. 30:22–25, 31:1–3.

Dr. Fraunfelder relied on an article by Suhler et al.,[38] of which he is also listed author, to describe the mechanism by which this occurs, a Type IV hypersensitivity reaction. Pet'r's Ex. 19 at 2; Pet'r's Ex. 19, Tab D at 4, ECF No. 81-4; *see also* Tr. 33:20–25, 34:1–3, 35:3–17. He argued that "vaccines are known to cause [T]ype IV hypersensitivity responses systemically." Pet'r's Ex. 19 at 2. Dr. Fraunfelder wrote that "all vaccinations, including [the] influenza vaccination, can cause a Type IV hypersensitivity reaction." Pet'r's Ex. 33 at 1 (citing Pet'r's Ex. 33, Tab A, ECF No. 82-1).[39] He explained that a Type IV hypersensitivity reaction alters the immune status of an individual and makes the patient "immunosuppressed." Tr. 43:21–25.

However, Dr. Fraunfelder acknowledged that "[t]he mechanisms underlying [T]ype IV hypersensitivity reactions are complex and not completely understood." Pet'r's Ex. 33 at 1. He relied on an article by Nussenblatt,[40] to explain that "Type IV hypersensitivity mechanisms (i.e., T-cell mediated) are of primary importance in the development if [sic] uveitis." *Id.*; Pet'r's Ex. 33, Tab C, ECF No. 82-3. Dr. Fraunfelder stated that the authors in this study "wanted to know [if] it is feasible that a systemically applied medicine like a vaccine given in your shoulder . . . could cause an inflammation inside the eye[.]" Tr. 37:17–20 (citing Pet'r's Ex. 33, Tab C). The authors examined "bovine models, rat models[,]" in which "they injected rats [] with retinal S-antigen systemically not in the eye but in the body." Tr. 37:21–24. The authors found that "this elicited a reaction in the eye which led to uveitis and blindness." Tr. 37:24–25. Nussenblatt explained that this occurs because "immune cells may 'home' to a target organ, [which] is in part due to the expression of HLA antigens on non-immune tissues in the eye." Pet'r's Ex. 33, Tab C at 2. This observation implicated the importance of T-cell mediation of diseases such as uveitis. *Id.* Nussenblatt based his conclusion, in part, on the efficacy of treatment of uveitis with anti-T-cell

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answered as either Yes, No, or "unknown." "Different point values (-1, 0, +1, or +2) are assigned to each answer." The questions include "are there previous conclusive reports of this reaction? Did the adverse event appear after the drug was given? Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was given? Did the adverse reaction reappear upon readministering the drug? Were there other possible causes for the reaction? Did the adverse reaction reappear upon administration of placebo? Was the drug detected in the blood or other fluids in toxic concentrations? Was the reaction worsened upon increasing the dose? Or, was the reaction lessened upon decreasing the dose? Did the patient have a similar reaction to the drug or a related agent in the past? Was the adverse event confirmed by any other objective evidence?" Total scores range from -4 to +13; the reaction is considered definite if the score is 9 or higher, probable if 5 to 8, possible if 1 to 4, and doubtful if 0 or less. *Adverse Drug Reaction Probability Scale (Naranjo) in Drug Induced Liver Injury,* NAT'L CENTER FOR BIOTECHNOLOGY INFO., https://www.ncbi.nlm.nih.gov (last visited Dec. 17, 2021).

[38] F.W. Fraunfelder, E.B. Suhler, et al., *Hepatitis B vaccine and uveitis: an emerging hypothesis suggested by review of 32 case reports*, 29:1 CUTANEOUS & OCULAR TOXICOL. 26–29 (2010).

[39] E. Chung, *Vaccine Allergies,* 3 CLIN. EXP. VACCINE RES. 50–57 (2014).

[40] R.B. Nussenblatt, *Basic and Clinical Immunology in Uveitis*, 31 J. OPHTHALMOL. 368–74 (1987).

drugs such as cyclosporine. *Id.* Dr. Fraunfelder opined that this study supports the fact that a Type IV hypersensitivity reaction occurs in the development of vaccine-caused uveitis. Tr. 37:14–16. He argued this "proves the theory in an animal model that a systemically applied immunization can cause a localized eye inflammation like uveitis." Tr. 38:1–3.

As further support, Dr. Fraunfelder relied on an article by Meng et al.,[41] to discuss the "critical" role of dendritic cells and T lymphocytes in Type IV hypersensitivity reactions. Pet'r's Ex. 33 at 1; Pet'r's Ex. 33, Tab B, ECF No. 82-2. The authors wrote that "[dendritic cells] take up and process complex antigens into short peptides which can be represented as peptide – HLA complexes on the surface of [dendritic cells] for T-cell recognition." Pet'r's Ex. 33, Tab B at 5. They continued that "[t]he interaction of T-cell receptors with peptide – HLA complexes determine the specificity of the response." *Id.* The authors went on to explain that "[d]rug-specific T cells have been detected in peripheral blood from hypersensitive patients . . . [e]ach T-cell subset can promote different types of inflammatory responses but also be able to counter-regulate each other." *Id.* Dr. Fraunfelder relied on the principles put forth in the Meng et al. article to argue that there is "an association between certain drug hypersensitivity reactions and specific HLA alleles, which could explain why the target organ for [Petitioner] was the eye." Pet'r's Ex. 33 at 1.

Dr. Fraunfelder relied on an article by Hassman et al.[42] to show that the flu vaccine can cause severe inflammation in the central nervous system, which can lead to infection with HSV and herpes encephalitis. Tr. 45:4–21 (citing Pet'r's Ex. 44 at 1, ECF No. 79-1). The authors noted that the flu vaccine triggered the reactivation of a latent HSV infection in 13 out of 38 million doses over ten years. Pet'r's Ex. 44 at 5. Dr. Fraunfelder testified that this occurs if the recipient experiences a "positive rechallenge" to prior flu vaccines. *See* Pet'r's Ex. 44 at 5; Tr. 45:4–21. He explained that "any time there is a rechallenge of a drug, like a vaccine being administered a second time and then that person gets a reaction again like they did the first time, that's called a positive rechallenge." Tr. 25:15–19. He continued that "if they get a positive rechallenge and they take [the drug] a second time and another positive rechallenge and they take it a third time, that's really strong evidence for a causal relationship with a drug and a side effect." Tr. 25:23–25, 26:1–2. Dr. Fraunfelder reiterated that a "positive rechallenge is relevant to an assessment of causation for a particular vaccine[.]" Tr. 25:12–14. He noted that the authors of the Hassman et al. study found that the patient developed retinitis each time that he received a vaccine. Tr. 45:16–17 (citing Pet'r's Ex. 44 at 1). Dr. Fraunfelder equated this to Petitioner's case and explained that this occurred because "the brain is considered a neurologic tissue in the area of the retina because the retina is contiguous with the nerves of the optic nerve and then the rest of the brain." Tr. 45:13–16. He therefore opined that this article provided "really strong evidence for the flu vaccine causing [central nervous system] side effects including retinitis[,] which is a type of inflammation like uveitis[,]" in Petitioner's case. Tr. 45:19–21. As further support, Dr. Fraunfelder noted that the Suhler et al.[43] study found one patient had "recurrent uveitis after both [the] second and third doses of [the Hep. B] vaccine." Tr. 25:10–11 (citing Pet'r's Ex. 19, Tab D). He also relied on an article

[41] X. Meng, et al., *Immunological Mechanisms of Drug Hypersensitivity*, 22:45 CURR. PHARM. DES. 6734–47 (2016).
[42] L.M. Hassman, et al., *Immunologic factors may play a role in herpes simplex virus 1 reactivation in the brain and retina after influenza vaccination,* 6 ID CASES 47–51 (2016).
[43] *See* Fraunfelder & Suhler, et al., *supra* note 38.

by Blanche et al.,[44] which discussed a 68-year-old woman who developed uveitis two days after her first flu vaccine. Tr. 27:23–25, 28:1–10 (citing Pet'r's Ex. 19, Tab B at 1, ECF No. 81-2). During his testimony, Dr. Fraunfelder cited an article by Knopf et al.,[45] as support for the notion of rechallenge based on its title, "Recurrent Uveitis After Influenza Vaccination." Tr. 28:16–17. He stated that the author "brings up the idea of 'immune priming' which is the idea that some event can make somebody susceptible to eye inflammation such as a trauma or a surgery or a vaccination." Tr. 28:19–25, 29:1. Under my questioning, Dr. Fraunfelder admitted that he did not know if Petitioner had ever received a flu vaccine prior to the one at issue. Tr. 55:17–25.

Regarding timing, Dr. Fraunfelder opined that "Type IV reactions usually occur days after a reaction." Tr. 41:4–5. He again relied on the Suhler et al.[46] article, which shows that uveitis caused by a Type IV hypersensitivity reaction "has occurred at time intervals of up to fifteen days post vaccination." Pet'r's Ex. 33 at 1; Pet'r's Ex. 33, Tab D. He stated that the authors found that "the mean number of days until uveitis was reported after a vaccination was three days. And the range was 1–15 days." Tr. 24:17–19. Dr. Fraunfelder opined that "[t]his [range] suggests that more than one mechanism is likely responsible." Pet'r's Ex. 33 at 1. He relied on an article by Wildner et al.,[47] to argue that "[s]everal peptides have been shown to induce uveitis via [molecular mimicry]." *Id.*; Pet'r's Ex. 33, Tab F, ECF No. 82-5. However, during his testimony, he abandoned his theory as it relates to molecular mimicry and instead proceeded on Type IV hypersensitivity only, "pick[ing one] pony[.]" *See* Tr. 33:22–25, 34:21.

He then addressed the time of onset in Petitioner's case. Dr. Fraunfelder opined that "[i]t is not insignificant that [Petitioner] had no [pre-existing] ocular complaints until nine days after her flu vaccination." Pet'r's Ex. 32 at 1 (citing Pet'r's Ex. 2 at 1). Dr. Fraunfelder testified that Petitioner's "uveitis probably began within a few days of the flu vaccine[]" at the time she developed a fever. Tr. 53:15–17. He stated that "[p]robably at the time that [Petitioner] presented with pain and redness and had partially systemic reaction with the fever and the cold [on November 12, 2012], that she probably had uveitis then[.]" Tr. 18:11–14. However, Dr. Fraunfelder opined that "it was unrecognized by her optometrist[.]" Tr. 18:14–15.

Dr. Fraunfelder explained that Petitioner "had symptoms that fits [sic] within the plausible biological mechanism of the type for hypersensitivity reaction, that she had symptoms within three days . . . and then, . . . many weeks later[,] that are consistent with uveitis related to the vaccine." Tr. 49:7–14. Dr. Fraunfelder relied on Petitioner's fever, redness, pain, and blurred vision beginning three days post vaccination to opine that a Type IV hypersensitivity reaction occurred. Tr. 38:18–22, 60:3–8. He posited that "in general, if it's a Type IV reaction, we should expect it within one day to three days, usually." Tr. 49:25, 50:1–2. He stated that Petitioner "was having a [Type IV hypersensitivity] reaction probably at day three[]" when she experienced a fever, which he opined, was consistent with the filed medical literature. Tr. 41:6 (citing Pet'r's Ex. 33, Tab D).

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[44] P. Blanche, et al., *Development of Uveitis Following Vaccination for Influenza,* 19:5 CLIN. INFECT. DIS. 979 (1994).

[45] Petitioner did not file the full article for consideration, it was merely cited in another exhibit. *See* Tr. 28:11–22; *see also* Pet'r's Ex. 19, Tab B.

[46] *See* Fraunfelder & Suhler, et al., *supra* note 38.

[47] G. Wildner, et al., *Autoimmune Uveitis Induced by Molecular Mimicry of Peptides from Rotavirus, Bovine Casein & Retinal S-Antigen*, 33 EUR. J. IMMUNOL. 2577–87 (2003).

Next, Dr. Fraunfelder responded to Dr. Bassiri's assertion that alternative causes could have been responsible for her injuries. He wrote that "Dr. Bassiri postulates on several anecdotes about what could have happened[,]" but Dr. Fraunfelder noted that he did not agree with Dr. Bassiri's proposals. Pet'r's Ex. 32 at 2. Dr. Fraunfelder agreed that Petitioner is "uniquely susceptible to herpes keratitis because . . . a person with [the] HLA-B27 haplotype do [sic] express herpes more than other people after having received an insult such as trauma or surgery, and, in this case, a vaccine." Tr. 39:8–13. He therefore opined that Petitioner was "immune primed" to develop herpes keratitis because of the uveitis and her positive HLA-B27 haplotype. Tr. 39:10–14. Dr. Fraunfelder wrote, however, that Dr. Bassiri "fail[ed] to consider [] that HLA-B27 status confers susceptibility and is not a determinant of disease[, a]s . . . many individuals who are HLA-B27 positive never go on to develop uveitis." Pet'r's Ex. 32 at 1. He stated that HLA-B27 is a "valid reason for uveitis, but in [Petitioner's] case it's more likely than not [sic] HLA-B27 as the primary cause for her uveitis." Tr. 47:11–13. Dr. Fraunfelder did not focus on whether HSV caused Petitioner's uveitis, as he postulated that her flu vaccine caused her uveitis and herpes keratitis. *See, e.g.*, Pet'r's Ex. 32 at 1. He did, however, state that a flu vaccine could be a trigger to reactivate a latent HSV infection. Tr. 44:8–10.

He then proposed a different alternative cause for Petitioner's uveitis and an explanation for her cold-like symptoms present on November 12, 2012. Tr. 45:22–25, 46:1–3. He stated "[i]t's possible . . . there's a syndrome that's well described from [the] flu vaccine called oculorespiratory syndrome." Tr. 46:1–3. Dr. Fraunfelder defined this condition as "a constellation of upper respiratory infectious signs. It's not infectious though. You might have a cough or a wheeze, stuffy nose. And then you also get uveitis." Tr. 46:6–9. He asserted that Petitioner's fever, cough, and cold symptoms reported during her November 12, 2012 appointment, could have been symptoms of oculorespiratory syndrome. Tr. 46:14–17.

On cross-examination, Dr. Fraunfelder conceded that he is not an expert in immunology or infectious diseases. Tr. 51:15–17, 52:5–7. Dr. Fraunfelder admitted that the Suhler et al.[48] article talks about the Hepatitis B vaccine, not the flu vaccine. Tr. 53:23–25. He agreed that the article noted '"there is a debate that uveitis occurs because of the [H]epatitis B infection.'" Tr. 54:15–17 (citing Pet'r's Ex. 19, Tab D). He also conceded that that particular article discussed a Type III hypersensitivity reaction, not a Type IV as initially postulated, which is the type of reaction that he maintained occurred in Petitioner's case. Tr. 54:1–3. When asked about the Benage[49] article, Dr. Fraunfelder maintained that the authors found an association between vaccines and the occurrence of uveitis and would not agree that the number of cases identified was small, noting "[t]hat's relative." Tr. 52:12–20. Dr. Fraunfelder agreed that Petitioner developed a herpes infection, and that they are usually either a primary infection or reactivation. Tr. 55:1–7. However, Dr. Fraunfelder was "not certain" whether Petitioner suffered a primary infection or reactivation of the herpes virus. Tr. 55:8–11.

Under my questioning, leaving the type of hypersensitivity reaction aside, I asked Dr. Fraunfelder to tell me what evidence he relied on to show that Petitioner experienced a hypersensitivity reaction, in general. Tr. 59–61. He first answered that he relied on her redness, pain, and loss of vision to indicate a Type IV hypersensitivity reaction occurred, but he later could

[48] *See* Fraunfelder & Suhler, et al., *supra* note 38.
[49] *See* Benage & Fraunfelder, *supra* note 35 at 1.

not point to specific evidence of a hypersensitivity reaction, generally. *See id.* In response, he stated he "just do[esn't] think that way," and instead arrived at the conclusion that Petitioner experienced a Type IV hypersensitivity reaction because of her delayed temporal response and "the number of days to onset[]" between her vaccination and onset of symptoms. Tr. 61:19–25, 62:1–15.

**2. Respondent's Expert, Dr. Bassiri**

Dr. Bassiri submitted three expert reports and testified during the hearing. Resp't's Exs. A, M, N; Tr. 64–135. He relied on his expertise in immunology and specialized knowledge in what makes patients predisposed to specific types of infections. Tr. 65–66. In his first expert report, Dr. Bassiri opined that there is no evidence of a causal relationship between the flu vaccine and Petitioner's condition. Resp't's Ex. A at 2. He wrote that Petitioner's flu vaccine "is exceedingly unlikely to have been the cause of the ensuing uveitis." *Id.* at 5.

First, Dr. Bassiri questioned Dr. Fraunfelder's reliance on the Benage[50] article to show a causal relationship between the flu vaccine and uveitis. *Id.* at 2. Dr. Bassiri explained that this article "revealed 28 cases of such an association" between vaccines and uveitis, "over a 30-year period (1984–2014)[.]" *Id.*; Resp't's Ex. C at 1, ECF No. 27-3. Dr. Bassiri stressed the significance of this statistical finding and argued that Dr. Fraunfelder has been unable to establish a causal link between the flu vaccine and uveitis, noting an association only. Resp't's Ex. M at 1, 2. Dr. Bassiri agreed that "there is entirely the possibility that things are associated," but stated that "if vaccines caused uveitis, [he] would [] expect to see a lot more cases[.]" Tr. 68:10–11, 22–24. He expressed that "we would probably see this more commonly than what Dr. Fraunfelder reported to us as 28 cases in 30 years." Tr. 69:12–14.

In response to the Benage article, Dr. Bassiri cited an article by Grajewski et al.,[51] in which the authors' findings '"argue against a substantial influence of allergies and atopy[52] on the onset of uveitis.'" Resp't's Ex. N at 1 (citing Resp't's Ex. O, ECF No. 52-2). The authors of the study examined patients with uveitis and some who were controls who did not have uveitis, to see if those with the condition had a significant disproportionately higher level of atopy or allergy to drugs. Resp't's Ex. O at 1. Dr. Bassiri explained that the authors found "there wasn't a [] statistically significant higher proportionate of atopy or allergy in the patients who [] develop uveitis." Tr. 78:12–15. Dr. Bassiri testified that the authors thought "that the presence of atopy or allergy was probably only minimally contributing to the development of uveitis." Tr. 78:16–18.

He wrote that "*associations* are frequently misinterpreted as evidence of *causal connections*." Resp't's Ex. A at 2 (emphasis in original). He emphasized that "association is strictly

[50] *See id*.
[51] R.S. Grajewski, et al., *Analysis of the impact of allergy and atopy on new onset of uveitis,* 95:3 ACTA OPHTHALMOL. 236–41 (2017).
[52] Atopy "refers to the genetic tendency to develop allergic diseases such as allergic rhinitis, asthma, and atopic dermatitis (eczema). Atopy is typically associated with heightened immune responses to common allergens, especially inhaled allergens and food allergens." AM. ACAD. OF ALLERGY, ASTHMA & IMMUNOLOGY, https://www.aaaai.org/Tools-for-the-Public/Allergy,-Asthma-Immunology-Glossary/Atopy-Defined (last visited Dec. 16, 2021).

that [] two events may have some type of temporal connection that lends one to believe that there may be an association between one event leading to the other." Tr. 67:9–12. He continued:

> [b]ut in reality[,] whenever one pairs a frequent event (in this case influenza vaccination) with an infrequent one (e.g., uveitis), in the absence of a clear and proven pathophysiologic and biological causal connection, the chances of the two events being causally related may be nil, and the existence of a causal relation must be interpreted with extreme caution. As an analogy, if earthquakes ("rare events") were to happen on cloudy days ("frequent events"), then one could claim the existence of an association between cloudy days and earthquakes. While this *association* would be true, the two events would not be *causally* connected.

Resp't's Ex. A at 2 (emphasis in original). He differentiated association from causation and noted that causation "is one in which there is a mechanistic description that fits one event directly leading to another and can be repeatedly elicited and more tested experimentally." Tr. 67:13–16.

On cross-examination, Dr. Bassiri admitted that hypersensitivity reactions, including Type IV, are "postulated" mechanisms in the literature of how uveitis can occur. Tr. 114:21–25, 115:1–3. However, Dr. Bassiri opined that Dr. Fraunfelder's proposed biological mechanism of causation, a Type IV hypersensitivity reaction, did not occur in Petitioner's case because neither the timing of onset nor the symptoms of her condition match what is understood about the mechanism. Resp't's Ex. A at 2–3; *see also* Tr. 94:19–20. Dr. Bassiri broke down the four types of hypersensitivity reactions. Tr. 69–70. He explained that the classification of the reaction depends on the onset time of the reaction, type of cellular involvement, and reactions to drugs or treatment meant to "block" the reaction. Tr. 70–71, 100:1–20. He noted that Type I hypersensitivity reactions "can be measured in seconds to minutes" and commonly occur in food allergies, which can be "deadly in the right setting." Tr. 70:1–7. Dr. Bassiri compared this to Type IV hypersensitivity reactions, in which "T cells . . . have seen an antigen, have seen that foreign particle previously presented to them in the context of another protein on the surface of cells . . . [a]nd then once they get re[-]exposed, they mount a reaction." Tr. 70:25, 71:1–6. Dr. Bassiri described a Type IV reaction as one which produces "a local inflammatory response[]" which "eventually dissipates[.]" Tr. 71:16, 72:18–19. He explained that the response dissipates because the antigens are eventually "metabolized, broken down, and they go away." Tr. 72:19–23. This is the type of reaction Dr. Bassiri would expect to see from a Type IV hypersensitivity reaction. Tr. 72:14–19. He stated that this response occurs "within about 24 hours . . . till about 48 hours[.]" Tr. 71:19–20. Dr. Bassiri testified that "[i]t's rarer that you have the delay result in occurrence of symptomatology much, much later like two to three weeks later." Tr. 73:14–16. To support his assertion, Dr. Bassiri relied on the article by Chung,[53] to show that "Type IV hypersensitivity reactions typically begin to manifest within 24–48 hours after antigen encounter (or immunization) and peak at 72–96 hours." Resp't's Ex. A at 3; Resp't's Ex. D at 2, ECF No. 27-4.

Dr. Bassiri noted that Type IV hypersensitivity reactions "are generally considered to be harmless." Resp't's Ex. N at 1 (citing Resp't's Ex. D at 2). He provided two common examples of

[53] *See* Chung, *supra* note 39.

Type IV hypersensitivity reactions, including poison ivy and a PPD test[54] for tuberculosis, which is read within 48 hours. Tr. 71–72. Dr. Bassiri placed "emphasis on the delayed being in contrast to the immediate seconds to minutes reaction that we expect with [Type I hypersensitivity] reactions." Tr. 72:9–12. Dr. Bassiri stated that there "should not [be] ongoing symptomatology [in a Type IV reaction] unless there's an alternative explanation." Tr. 75:15–17.

Regarding the onset of symptoms, Dr. Bassiri wrote that "Type IV hypersensitivity [reactions] would not typically present as a 'stye'" as it did in Petitioner's case. Resp't's Ex. A at 3. He testified that the tenderness noted along Petitioner's cheeks or nose during her November 12, 2012 appointment with Dr. Alvarez "would be atypical for a delayed-type hypersensitivity reaction." Tr. 74:6–10. Dr. Bassiri also noted that Petitioner reported a fever several days post vaccination. Resp't's Ex. A at 3 (citing Pet'r's Ex. 16 ¶ 4). He continued that "[T]ype IV hypersensitivity is rarely associated with fever – especially when the inoculum size of the antigen (e.g., that in influenza vaccines) is small." Resp't's Ex. M at 2; Tr. 73:1–6. He elaborated that "[v]ery rarely does [a Type IV reaction] involve systemic signs where somebody gets febrile, feels ill." Tr. 73:2–3. Dr. Bassiri opined that "[w]hile fever can occur with severe and systemic Type III hypersensitivity reactions (such as Serum Sickness), it is otherwise not typical in Type III and Type IV hypersensitivity responses[.]" Resp't's Ex. A at 3; *see also* Tr. 106:16–22. He agreed that a fever could occur in a Type IV hypersensitivity reaction "if you were to give somebody who has a prior sensitization a large amount of that antigen, you would have a relatively large or robust immune response[,] . . . the end result of which could be fever." Tr. 107:2–8. Dr. Bassiri testified that he did not see the level of systemic response in Petitioner that he would expect to see to suggest that a fever was a part of her hypersensitivity reaction. Tr. 130:11–20. He noted that Petitioner was not "otherwise manifesting signs and symptoms of a severe hypersensitivity reaction." Resp't's Ex. A at 3. As an example, Dr. Bassiri testified he would have expected to see signs of liver or kidney dysfunction if Petitioner actually experienced a Type IV or even Type III hypersensitivity reaction. Tr. 115:18–25. Dr. Bassiri agreed with Dr. Fraunfelder that it is oftentimes difficult to classify a particular outcome with a particular type of hypersensitivity reaction. Tr. 98:4–6. But he maintained that "widespread used tests" could have been used in Petitioner's case to determine the type of hypersensitivity reaction, but they were not done. Tr. 98:23–25, 99:1–2.

On cross-examination, Dr. Bassiri addressed the Meng et al.[55] article, which stated '"delayed type reactions present with much more complex clinical phenotypes ranging from mild skin reactions to life-threatening reactions.'" Tr. 101:1–4 (citing Pet'r's Ex. 33, Tab B). Dr. Bassiri agreed that "that can occur[]" and that Type IV hypersensitivity reactions are more "heterogenous" than Type I or II reactions. Tr. 101:5–10. He explained this is possible because there are "a variety of different mechanisms in play . . . that lead to a variety of different . . . side effects[]" depending on the individual and the formulation of the drug. Tr. 101:11–21, 102:2–3. He agreed that a positive

[54] Dr. Bassiri defined a PPD test as one that "test[s] for exposure to tuberculosis in which a small needle is used to insert under the skin and antigens or foreign materials that are very similar to the components of the tuberculosis. And what is measured is the actual response." Tr. 71:9–13. He explained that "if someone has seen TB before and they have generated T cells that are responsive against TB, what happens in them is you get an inflammatory response that can actually be measured . . . within about 24 hours." Tr. 71:13–19.

[55] *See* Meng, et al., *supra* note 41 at 1.

HLA status can also provoke a different reaction. Tr. 102:20–23. Dr. Bassiri maintained that a Type IV hypersensitivity reaction did not occur in Petitioner's case. Tr. 116–117.

Dr. Bassiri disagreed with Dr. Fraunfelder's statement that "'all vaccinations, including [the] influenza vaccination, can cause a Type IV hypersensitivity reaction.'" Resp't's Ex. N at 1 (citing Pet'r's Ex. 33 at 1). Dr. Bassiri relied on the same Chung[56] article to show that "nowhere in this article is it stated that all vaccines can cause *Type IV hypersensitivity*." Resp't's Ex. N at 1 (emphasis in original) (citing Resp't's Ex. D at 1). He continued that while the article does indicate that "'[a]lmost all the vaccine components can be considered as potential triggers of an allergic reaction,'" this "general statement [] does not suggest that all vaccines cause Type IV hypersensitivities." *See id.*

Under my questioning, I asked Dr. Bassiri whether it was possible for a patient to develop a Type IV hypersensitivity reaction without exposure to the vaccine, but through exposure to the wild virus itself. Tr. 133:5–8. He explained that "[o]ftentimes when you've been exposed to the wild-type virus, you develop a robust enough T cell response so that if you are exposed again you never even become symptomatic." Tr. 134:8–11. He continued that a patient "might never even know that you were re-exposed because you have antibodies that bind those viruses and clear them from your system . . . with what are called memory T cells that are formed that can then much more rapidly take care of any replicating virus." Tr. 134:12–17.

Dr. Bassiri was asked about Dr. Fraunfelder's reliance on the Hassman et al.[57] article. Tr. 79–80 (citing Pet'r's Ex. 44). He stated that this article is "an example" of "the causal relationship, especially with the positive – [] positive sort of development in a temporal fashion" of HSV and herpes encephalitis following a flu vaccine. Tr. 79:3–8. However, Dr. Bassiri highlighted some distinctions between the article and Petitioner's case. Tr. 79:9. He noted that the article examined a patient with a pre-existing "immune defect or immune dysregulation." Tr. 79:14–15. Dr. Bassiri stated that there is no evidence that Petitioner suffered from an immune defect. Tr. 79:18–20. He also pointed out that the patient in the article had "repeated reactions" to the vaccines he received. Tr. 80:7–9. Dr. Bassiri testified that Petitioner "had at least checked a box" indicating that she had never had a prior reaction to a flu vaccine. Tr. 79:24–25, 80:1–7 (citing Pet'r's Ex. 1 at 1). Dr. Bassiri noted that he did not know how many flu vaccines Petitioner had received in the past, but he knew she had received at least one based on the contents of the same medical record. Tr. 132:1–15 (citing Pet'r's Ex. 1 at 1).

He addressed the London et al.[58] article relied upon by Dr. Fraunfelder. Tr. 80:20–25 (citing Pet'r's Ex. 45). He noted that the article rated associations between the administration of a drug, such as the flu vaccine, and adverse reactions, such as uveitis, using the Naranjo scale. Tr. 81:1–8. While the authors came up with an association of "probable" (score of 7) between the flu vaccine and uveitis in a general sense, Dr. Bassiri used the same scale and applied it to the facts of Petitioner's case. Tr. 81:9–11. He stated that "if [he] were to go through and score each one of the criteria for her specific case, actually the value that would be derived and – and generously giving

[56] *See* Chung, *supra* note 39.
[57] *See* Hassman, et al., *supra* note 42 at 1.
[58] *See* London, et al., *supra* note 36 at 1.

points to her case would be a value of 3,[59] which would put it in the 'possible,' but not the 'probable' range." Tr. 81:12–17. He opined that the main reason for the discrepancy is that the authors only analyzed "a general guideline" and did not consider the alternative explanations in the case of Petitioner. Tr. 81:18–22. Dr. Bassiri stated that "quite frankly, those alternative explanations are much more commonly accepted as a reason for developing uveitis[.]" Tr. 81:23–25.

Dr. Bassiri questioned Dr. Fraunfelder's conclusion that Petitioner had uveitis during her November 12, 2012 appointment with Dr. Alvarez instead of bacterial conjunctivitis, for which she was treated. Resp't's Ex. M at 1. He also criticized Dr. Fraunfelder's assertion that Petitioner "had developed uveitis 'well before the[ January 7, 2013] findings,'" because he failed to provide "distinct data or proof of this statement." Resp't's Ex. A at 3 (citing Pet'r's Ex. 19 at 1). Dr. Bassiri wrote that "it is [] difficult to conclusively know when the uveitis may have started." Resp't's Ex. A at 3. Dr. Bassiri "emphasized that the signs and symptoms consistent with uveitis were not documented in [Petitioner] until [January 7, 2013], over two months after her influenza immunization." *Id*. On cross-examination, Dr. Bassiri testified that the symptoms "consistent" with uveitis "include things like redness of the eye and pain[.]" Tr. 108:6–13. He admitted that Petitioner's record from November 12, 2012, shows she was experiencing redness and pain during that appointment. Tr. 108:14–16 (citing Pet'r's Ex. 2 at 1). He further admitted that Petitioner's affidavit indicates she experienced those same symptoms "contemporaneous with her fever[,]" three days post-vaccination. Tr. 108:17–21 (citing Pet'r's Ex. 16 at 1). Dr. Bassiri stated that Petitioner's fever, eye pain, and redness occurred approximately three to four days post vaccination. Tr. 117:11–14.

He stated that a Type IV hypersensitivity reaction occurs "within about 24 hours . . . till about 48 hours[.]" Tr. 71:19–20. Dr. Bassiri testified that "[i]t's rarer that you have the delay result in occurrence of symptomatology much, much later like two to three weeks later." Tr. 73:14–16. Based on this, Dr. Bassiri wrote "it is just as reasonable to postulate that other etiologies led to the development of uveitis in [Petitioner] after the closing of what would be considered a reasonable window within which to implicate the involvement of the influenza vaccine." Resp't's Ex. A at 3.

Next, Dr. Bassiri indicated that there are "multiple alternative" causes for the development of uveitis in Petitioner's case. Resp't's Ex. M at 2. He wrote that while Dr. Fraunfelder "postulated a causal connection for the [] association between influenza vaccination and development of

[59] Dr. Bassiri went through each of the Naranjo criteria as it pertained to Petitioner. He awarded a "plus 1" in response to the first criteria, as there are previous reports of the occurrence of this reaction. Tr. 82:11–14. He awarded a "plus 2" in response to the second criteria, as the adverse event happened after administration of the drug (the flu vaccine). Tr. 82:16–18. He awarded a "no" or "not known" (equivalent to a value of "zero") in response to the third criteria regarding whether the adverse reaction improved after the drug was discontinued, as it was only given once. Tr. 82:19–25. The drug was not re-administered, so he awarded a "zero" for criteria four. Tr. 83:1–4. Criteria five addressed alternative causes, which he awarded a "minus 1" since he has posited alternative causes for Petitioner's condition. Tr. 83:5–9. He awarded scores of "zero" for criteria six through eight, as Petitioner never received a placebo, the flu vaccine is not known to be "toxic," and she never received a higher or lower dosage of the vaccine. Tr. 83:10–25. He awarded a zero in response to the ninth criteria based on Petitioner's history of no adverse reactions following prior flu vaccines. Tr. 83:24–25, 84:1–4. He awarded a "plus 1" in response to the tenth criteria, citing the objective evidence of uveitis noted by Dr. Foote on January 7, 2013. Tr. 84:5–10.

uveitis, he has not excluded any other possibilities that are known to be causally-related common causes of uveitis." Resp't's Ex. A at 3. Dr. Bassiri considered two "[o]ther etiologies that much more commonly result in the development of uveitis[.]" *Id.* at 3–4 (emphasis in original). First, Dr. Bassiri discussed the fact that Petitioner "was noted to carry the HLA-B27 allele[.]" *Id.* at 4 (citing Pet'r's Ex. 5 at 15). He wrote that "[c]arriers of the HLA-B27 allele have a significantly elevated frequency of developing recurrent uveitis." Resp't's Ex. A at 4. He stated that this is relevant in Petitioner's case because "HLA-B27 is highly associated with the possibility of development of a number of autoimmune diseases including uveitis[.]" Tr. 86:3–8. He relied on an article by Wakefield et al.,[60] to show that "HLA-B27-mediated uveitis accounts for 18–32% of all cases of anterior uveitis[.]" Resp't's Ex. A at 4; Resp't's Ex. K, ECF No. 27-11. On cross-examination, he admitted that a majority of people that are HLA-B27 positive "never go on to develop uveitis." Tr. 112:3–8. However, he noted that the authors of the Wakefield et al. article still found that 20% of HLA-B27 positive patients do develop uveitis, which is "still quite significant." Tr. 112:14–19 (citing Resp't's Ex. K). Dr. Bassiri explained that in order for HLA-B27 uveitis to manifest, "it depends on [an] environmental factor," which could include infections or "vaccination . . . in the right setting." Tr. 112:9–12, 20–24.

Dr. Bassiri addressed the possible mechanism responsible for Petitioner's HLA-B27 haplotype causing her uveitis. Tr. 84:20–25, 85:1–3. He explained that "immunologists think that HLA-B27 may be resulting in predisposition to a variety of autoimmune phenomen[a], including uveitis." Tr. 85:1–3. He noted this is possible because of molecular mimicry whereby "the HLA-B27 can present certain parts of antigens or foreign materials in a way that makes it appear to the T cells that those are similar to self-proteins or self-antigens. And those T cells then inappropriately would attack those self-tissues[.]" Tr. 85:5–9. Dr. Bassiri also explained that there is evidence that the HLA-B27 molecule itself can elicit a response in cells when it goes through the process of "getting folded." Tr. 85:11–14. He continued that the "folding can actually set off focal inflammatory signaling by cells. And if you have enough of it going on, that could predispose to initiation of an inflammatory cascade even in the absence of an actual trigger." Tr. 85:14–18. He added one other possibility is that pieces of the HLA-B27, "which eventually get expressed onto cell surfaces could . . . come together in an inappropriate manner that actually ends up allowing inflammatory ligons [sic] on other cells to bind them and start an inflammatory cascade, again, in the absence of a specific trigger." Tr. 85:19–25, 86:1–2.

Dr. Bassiri also wrote that "reactivation [of HSV] is known to cause uveitis and neurotrophic keratitis." Resp't's Ex. M at 2; Resp't's Ex. A at 4; *see also* Resp't's Ex. F at 1, ECF No. 27-6.[61] He provided medical literature supporting this conclusion. Resp't's Ex. A at 4 (citing Resp't's Ex. J at 1, ECF No. 27-10.[62]). The Tsirouki et al. article noted that "[h]erpes and toxoplasmosis are the leading infectious causes of uveitis." Resp't's Ex. J at 1. Based on this, Dr. Bassiri posited that he is "not sure why one would invoke an unproven association as being the cause of [Petitioner's] uveitis." Resp't's Ex. M at 2. He postulated that "even if [Petitioner's] HLA-

[60] D. Wakefield, et al., *What is New HLA-B27 Acute Anterior Uveitis,* 19 OCULAR IMMUNOL. & INFLAMMATION 139–144 (2011).
[61] S.B. Engelhard, et al., *Infectious Uveitis in Virginia,* 9 CLIN. OPHTHALMOL. 1589–94 (2015).
[62] T. Tsirouki, et al., *A Focus on the Epidemiology of Uveitis,* 0:0 OCULAR IMMUNOL. & INFLAMMATION 1–15 (2016).

B27, which is also independently a risk factor for uveitis, were not the cause of her uveitis, then her proven HSV disease very easily could have been." *Id.*

Dr. Bassiri opined that Petitioner's herpesvirus preceded her uveitis and subsequent herpes keratitis. Tr. 86:11–14. Dr. Bassiri relied on Petitioner's fever and "mild cold" symptoms noted several days post vaccination to support his assertion that Petitioner experienced either a primary or reactivated herpesvirus instead of uveitis at that time. Resp't's Ex. A at 4 (citing Pet'r's Ex 2 at 1). He stated that in both the primary and reactivation of herpesviruses, "one can see systemic signs of [] an illness, such as fever." Tr. 75:4–5. Dr. Bassiri also focused on the tenderness noted in Petitioner's nose during her November 12, 2012 appointment, and stated that it is relevant because in the reactivation of herpesvirus, itchiness or irritation can be found. Tr. 74:20–25. Maintaining that Petitioner's symptom presentation did not fit that of a Type IV hypersensitivity reaction, Dr. Bassiri opined that Petitioner's cold symptoms during her November 12, 2012 appointment with Dr. Alvarez "point towards an alternative hypothesis [] by which this damage occurred to her, . . . instead of [] the vaccine induc[ing] a delayed-type hypersensitivity, which resulted in uveitis . . . ." Tr. 76:1–5. He testified that "the possibility exists that she could have had a herpesvirus infection that then presented as uveitis." Tr. 76:7–9. He nonetheless agreed that other than her fever mentioned during her November 12, 2012 appointment, Petitioner did not report any other cold or flu-like symptoms during November of 2012, or subsequent visits in early 2013. Tr. 104:11–16, 105–106 (citing Pet'r's Ex. 2 at 1; Pet'r's Ex. 16 at 1; Pet'r's Ex. 38 at 1A).

Dr. Bassiri cited two articles by Darougar & Wishart et al.,[63] to explain that "these [cold] symptoms are common findings accompanying either primary or reactivation [of] herpesvirus ocular infections." Resp't's Ex. A at 4; Resp't's Ex. E at 1, ECF No. 27-5; Resp't's Ex. L at 2, ECF No. 27-12; *see also* Tr. 75:17–22. The authors found that in primary herpesvirus ocular infections, upper respiratory tract "cold" symptoms are observed in 35% of patients, with fever in 31% of cases. Resp't's Ex. E at 1. They compared that to reactivated herpesvirus ocular infections and found such upper respiratory tract or cold symptoms increases and occurs in 48% of cases. Resp't's Ex. L at 2.

He focused on Petitioner's stye diagnosis on November 12, 2012. Resp't's Ex. A at 4 (citing Pet'r's Ex. 2 at 1). Dr. Bassiri opined that this was a manifestation of Petitioner's herpesvirus and should not have been diagnosed as a stye by Dr. Alvarez. *See id.* He posited that this misdiagnosis occurred "due to the presence of pustules instead of clear-fluid filled vesicles." Resp't's Ex. M at 2. Dr. Bassiri relied on the same Darougar & Wishart et al.[64] articles, in which the authors found "15 and 23% of patients with primary or reactivation herpesvirus ocular infections displayed chronic blepharitis (inflammation of the eyelid margin)." Resp't's Ex. A at 4. Dr. Bassiri concluded that based on "[t]he cadence of what happened to [Petitioner], the presence of systemic signs and symptoms of disease [fever], and then the focal signs and symptoms of the disease making you think that there probably are alternative explanations as to what actually happened to her." Tr. 74:15–19.

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[63] S. Darougar & M.S. Wishart, et al., *Epidemiological and clinical features of primary herpes simplex virus ocular infection,* 69 BR. J. OPHTHALMOL. 2–6 (1985); M.S. Wishart & S. Darougar, et al., *Recurrent herpes simplex virus ocular infection: epidemiological and clinical features,* 9 BR. J. OPHTHALMOL. 669–72 (1987).

[64] *See id.*

Dr. Bassiri addressed the possible mechanism responsible for Petitioner's herpesvirus ocular infection causing her uveitis. Resp't's Ex. A at 5. He wrote that "viral illnesses, via molecular mimicry, are frequently postulated to be triggers for development of autoimmune phenomena such as uveitis." *Id.* Dr. Bassiri testified that Petitioner experienced a herpesvirus which led to uveitis, as herpesviruses can affect "immunocompetent and immunocompromised hosts[]" and one does not "have to have a defect in [the] immune status to be infected and/or to actually have reactivation of the disease." Tr. 86:15–19. Dr. Bassiri stated that while it is true that people are "more prone" to reactivation of latent viruses, including HSV, if they are immunocompromised, "you don't need to have that." Tr. 94:1–3. He testified that the reactivation of HSV can occur in "immunocompetent hosts that [] reactivate their herpesvirus family." Tr. 94:3–5. Dr. Bassiri agreed that "severe stress can induce immune dysfunction which can predispose to the possibility of reactivation of herpesviruses." Tr. 109:18–21. He opined that it is possible, but rare, that a vaccine could also reactivate a latent HSV infection. Tr. 110:18–22. He posited that if that occurrence was common, however, "we would probably stop giving [the] influenza vaccination to immunocompromised hosts[.]" Tr. 110:23–25. Dr. Bassiri agreed that it would be difficult to determine who susceptible people would be before receipt of the vaccine. Tr. 111:4–7.

Dr. Bassiri noted the fact that viral illnesses are triggers for development of an autoimmune phenomena such as uveitis is significant in Petitioner's case because she has a family history consisting of a sister with possible rheumatoid arthritis and a son with possible ankylosing spondylitis. Resp't's Ex. A at 5. He wrote that this suggests "a relatively strong predisposition to autoimmune diseases." *Id.* He also testified that a positive HLA-B27 haplotype may result in a predisposition to a variety of autoimmune phenomenon, including uveitis. Tr. 85:1–3. Dr. Bassiri concluded that given Petitioner's predisposing family history, her positive ANA, and HLA-B27 allele, "it would be reasonable to wonder if she already had a genetic predisposition to autoimmunity that may have led to development of uveitis triggered by a viral infection." Resp't's Ex. A at 5; *see also* Tr. 77:6–20.

Next, Dr. Bassiri highlighted that Dr. Fraunfelder failed to differentiate whether Petitioner suffered from a primary infection or a reactivation of a latent HSV infection. Resp't's Ex. N at 2. Dr. Bassiri explained that this differentiation is an "important distinction and not merely semantics[.]" *Id.* He argued that this omission makes Dr. Fraunfelder's proposed theory that Petitioner suffered from an altered immune status that led to her susceptibility of HSV disease and herpes keratitis, "extremely confusing from an immunological and infectious disease perspective." *Id.* Dr. Bassiri explained that if Petitioner experienced an HSV infection as he posited, Dr. Fraunfelder's theory of altered immunity does not make sense because "you don't need to have altered immunity in order to develop HSV infections and [] recrudescence [there]of." Tr. 93:22–25. He noted that Petitioner did not have an altered immunity. Tr. 87:2–5. He continued that "the pathogenesis of neither primary nor reactivation [of] HSV disease is consistent with uveitis resulting in infection[.]" Resp't's Ex. N at 2.

Dr. Bassiri admitted that it is "difficult" to know if Petitioner, in fact, had a primary disease. Tr. 90:9–10. However, he stated it is "entirely more likely because of [] epidemiologically that she had been exposed to herpesviruses previously." Tr. 90:10–12. Dr. Bassiri noted that Dr. Fraunfelder seems to posit that Petitioner "suffered from a primary infection (as suggested by his

claim that she had no prior history of herpes zoster)[.]" Resp't's Ex. N at 2 (citing Pet'r's Ex. 33 at 3). Dr. Bassiri argued that if this was true, "there would be no reason to implicate altered immunity in the pathogenesis of this infection, as primary HSV infections happen very commonly in healthy[,] non-immunosuppressed individuals[.]" Resp't's Ex. N at 2. Dr. Bassiri also argued that if Dr. Fraunfelder asserted that Petitioner suffered from a reactivation of a latent infection, "this commonly occurs in immunosuppressed patients. Yet, [Petitioner] was not on any immunosuppressive medications[.]" *Id.* He continued that even if Petitioner "were somehow immunosuppressed, it is unclear why immunosuppression would be associated with T cell activation (which is a requisite for development of a Type IV hypersensitivity)[.]" *Id.* He testified that a Type IV hypersensitivity reaction would not lead to an altered immune system. Tr. 92–93. He noted that "in fact, hypersensitivity reactions are commonly *treated* by giving immunosuppressive medications." Resp't's Ex. N at 2 (emphasis in original). Dr. Bassiri concluded that "Dr. Fraunfelder's proposed mechanism for development of uveitis is not consistent with either type of HSV infection." *Id.* Instead, Dr. Bassiri proposed that "what is significantly more likely is [a] HSV infection resulting in uveitis[.]" *Id.* Overall, he concluded that "the simplest explanation here is that [Petitioner's] HLA-B27 and/or herpesvirus infection, which are well-known to be associated with uveitis, possibly led to her uveitis . . . ." Tr. 82:2–4.

While Dr. Bassiri maintained that Petitioner did not experience a hypersensitivity reaction following the flu vaccine, he addressed Dr. Smith's note from November 4, 2016. Tr. 119:19–22 (citing Pet'r's Ex. 30 at 1). The note indicated that Petitioner was "given a skin test for TB[,] has had a BCG shot before [and] ha[d an] enormous reaction and since then her eyes are flaring." Tr. 119:24, 120:1–2. The note cautioned Petitioner '"to avoid all things that stimulate dendritic cells[,] which is vaccines and BCG as it activates her eye disease."' Tr. 120:4–6 (citing Pet'r's Ex. 30 at 1). He admitted that this warning could have possibly been an indication that Dr. Smith believed Petitioner had a hypersensitivity reaction to the TB test. Tr. 122:24–25, 123:1, 124:18–24. Dr. Bassiri, however, noted that Petitioner did not have a reaction to the BCG as a child or the skin test in 2012, but did have a reaction in 2016. Tr. 120:7–9. He explained that one reason this could have happened is that "people who receive the BCG in their initial phase will not have a response to that BCG vaccine. But when [] they have follow-up PPDs, they can have a response to that." Tr. 123:11–14. He could not opine as to what caused Petitioner's flare in 2016, and could therefore not determine if it was, in fact, a hypersensitivity reaction. Tr. 122:11–22. He acknowledged that Petitioner's symptom presentation was described as "waxing and waning[.]" Tr. 123:1–2. But opined that "all that says is that it gets better and worse potentially depending on what sort of medication she's on." Tr. 123:2–5.

He acknowledged Petitioner's negative Varicella Zoster virus ("VZV") antibody test in January of 2011, prior to the onset of her injury, and compared it to the "+Abs" notation in her records from Norway in August of 2013. Resp't's Ex. A at 4 (citing Pet'r's Ex. 8 at 7). He noted that while she was tested for VZV in January of 2011, Petitioner was not tested for HSV. Tr. 90:15–16. He wrote that "Dr. Ostern's [August 2013] note from Norway reports that specimens from the cornea and anterior chamber were negative for viruses, bacteria, and fungi[.]" Resp't's Ex. A at 4 (citing Pet'r's Ex. 11 at 1). As an explanation for the negative test, Dr. Bassiri opined that "these samples had been obtained well after several rounds of therapy with multiple topical and systemic antibiotics and antivirals." Resp't's Ex. A at 4; *see also* Tr. 91:1–13. He relied on an

article by Tsatsos et al.,[65] to explain that "[i]f herpesviruses such as HSV or VZV were the etiology for [Petitioner's] uveitis and keratitis, then it is possible that some of the damage may have been mitigated by the continued use of appropriate antivirals[.]" Resp't's Ex. A at 4; Resp't's Ex. I, ECF No. 27-9.

On cross-examination, Dr. Bassiri reiterated that the mechanism linking vaccines and uveitis has not been proven. Tr. 96:19–20. When asked what evidence he would require to prove the mechanism linking vaccines to uveitis, Dr. Bassiri stated that "since obviously one cannot experiment on humans[,]" he would require animal models. Tr. 96:23–25, 97:1–4. Dr. Bassiri addressed the Nussenblatt[66] article containing an animal model proffered by Dr. Fraunfelder. Tr. 97:5–6. He testified that he did not place a lot of stock in this animal study. Tr. 131:16–19. Dr. Bassiri did not agree that the study supports the role of hypersensitivity reactions in the development of uveitis. Tr. 97:11–18. Instead, he stated the study indicates "what we sort of expect the immune system to do, which is that if you immunize an animal or human to a particular piece of the body, that you could break what's called tolerance . . . and induce a response [] against self-antigens." Tr. 97:14–18, 98:1–2, 132:1–3. However, when pressed, he acknowledged that the Nussenblatt[67] article showed support for a Type IV hypersensitivity reaction causing uveitis in an animal model. Tr. 115:3–7.

Under my questioning, Dr. Bassiri stated that it does not matter whether Petitioner had a primary or latent HSV infection. Tr. 125:3–8. He testified that while both forms are associated with the development of uveitis, a reactivation is "probably much more likely because . . . the prevalence of people who have HSV as part of them is much larger than the people who acquire it on a yearly basis[.]" Tr. 125:9–13. He clarified that, independent of a positive HLA-B27 status, one can experience the reactivation of HSV and develop uveitis. Tr. 125:22–25. He stated that the converse is also true, "[i]f you have HLA-B27 independent of HSV, you can have uveitis." Tr. 126:2–3. Dr. Bassiri stressed that in Petitioner's case, "both of those are playing a role[]" and are known causes. Tr. 126:4–11. He emphasized that these are not merely known associations of uveitis but known causes. Tr. 126:7–14. He concluded that Petitioner was "prone for [uveitis] to happen at any point. And just because it happened after she received her [flu] vaccination is almost always agnostic to that." Tr. 126:18–20.

I asked Dr. Bassiri to tell me why, while he did not agree, did Petitioner have more than one treater opining that she experienced a hypersensitivity reaction to the vaccine and therefore cautioned her not to get further vaccinations. Tr. 128:14–25, 129:1–5 (citing Pet'r's Ex. 30 at 1). He stated that he was "not entirely sure about that." Tr. 129:18.

## IV. Applicable Legal Standards

To receive compensation under the Vaccine Act, a petitioner must demonstrate either that: (1) the petitioner suffered a "Table injury" by receiving a covered vaccine and subsequently developing a listed injury within the time frame prescribed by the Vaccine Injury Table set forth

[65] M. Tsatsos, et al., *Herpes Simplex Virus Keratitis: an update of the pathogenesis and current treatment with oral and topical antiviral agents,* CLIN. EXP. OPHTHALMOL. (2016).
[66] *See* Nussenblatt, *supra* note 40 at 1.
[67] *See id.*

at 42 U.S.C. § 300aa-14, as modified by 42 C.F.R. § 100.3; or (2) that petitioner suffered an "off-Table injury," one not listed on the Table, as a result of his receiving a covered vaccine. *See* 42 U.S.C. §§ 300aa-11(c)(1)(C); *Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Hum. Servs.*, 440 F.3d 1317, 1319-20 (Fed. Cir. 2006). Petitioner does not allege a Table injury in this case; thus, she must prove that her injury was caused-in-fact by a Table vaccine.

To establish causation-in-fact, a petitioner must demonstrate by a preponderance of the evidence that the vaccine was the cause of the injury. 42 U.S.C. § 300aa-13(a)(1)(A). A petitioner is required to prove that the vaccine was "not only a but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321–22 (quoting *Shyface v. Sec'y of Health & Hum. Servs.*, 165 F.3d 1344, 1352–53 (Fed. Cir. 1999)).

In the seminal case of *Althen v. Sec'y of the Dept. of Health & Hum. Servs*, the Federal Circuit set forth a three-pronged test used to determine whether a petitioner has established a causal link between a vaccine and the claimed injury. *See* 418 F.3d 1274, 1278–79 (Fed. Cir. 2005). The *Althen* test requires petitioners to set forth: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id.* at 1278. To establish entitlement to compensation under the Program, a petitioner is required to establish each of the three prongs of *Althen* by a preponderance of the evidence. *Id.* "[C]lose calls regarding causation are resolved in favor of injured claimants." *Id.* at 1280. Further, evidence used to satisfy one prong of the test may overlap to satisfy another prong. *Capizzano,* 440 F.3d at 1326.

A petitioner who satisfies all three prongs of the *Althen* test has established a prima facie showing of causation. *Hammitt v. Sec'y of Health & Hum. Servs*., 98 Fed. Cl. 719, 726 (2011). A petitioner who demonstrates by a preponderance of the evidence that he suffered an injury caused by vaccination is entitled to compensation unless the respondent can demonstrate by a preponderance of the evidence that the injury was caused by factors unrelated to the vaccination. *See Althen*, 418 F.3d at 1278; *Knudsen v. Sec'y of Health & Hum. Servs.*, 35 F.3d 543, 547 (Fed. Cir. 1994). In such a case, the government must not merely prove the existence of an alternative cause, but that such an alternative actually caused the injury. *Knudsen,* 35 F.3d at 549. Consequently, when and if Petitioner establishes a prima facie case, the burden then shifts to the government to prove that an alternative cause, unrelated to the administration of the vaccine, was the "sole substantial factor" in causing the alleged injury. *See de Bazan v. Sec'y of Health & Hum. Servs.*, 539 F.3d 1347, 1354 (Fed. Cir. 2008); *see also Hammitt*, 98 Fed. Cl. at 726 (explaining that the respondent's burden is to show that the "factor unrelated" was the "sole substantial factor" in causing the injury). Additionally, a factor unrelated "may not include 'any idiopathic, unexplained, unknown, hypothetical, or undocumentable cause, factor, injury, illness or condition.'" 42 U.S.C. § 300aa-13(a)(2); *see also Doe v. Sec'y of Health & Hum. Servs.*, 601 F.3d 1349 (Fed. Cir. 2010) (opining that an idiopathic diagnosis cannot be a "factor unrelated," as it is idiopathic).

In considering the reliability of a petitioner's evidence of a prima facie case, the special master may consider alternative causes for a petitioner's condition that are reasonably raised in the

record, even if the respondent does not pursue a formal alternative cause argument. *Doe,* 601 F.3d at 1358. Thus, in weighing a petitioner's case-in-chief, a special master may consider evidence that the petitioner's alleged injury could have been caused by alternative causes. *Id.* Proof of a "logical sequence of cause and effect" will eliminate potential likely alternatives. *Walther v. Sec'y of Health & Hum. Servs.*, 485 F.3d 1146, 1151 (Fed. Cir. 2007).

## V. Discussion

### A. Petitioner's Diagnoses

As a factual predicate to proving vaccine-causation, it is Petitioner's burden to demonstrate that she actually suffers from the injuries alleged to have been caused by her November 3, 2012 flu vaccination. *See Hibbard v. Sec'y of Health & Hum. Servs.*, 698 F.3d 1358, 1364–65 (Fed. Cir. 2012); *Lombardi v. Sec'y of Health & Hum. Servs.*, 656 F.3d 1343, 1353 (Fed. Cir. 2011); *Broekelschen v. Sec'y of Health & Hum. Servs.*, 618 F.3d 1339, 1346 (Fed. Cir. 2010) (finding that in a case where the injury itself is in dispute, it is appropriate for the special master to "first determine which injury was best supported by the evidence presented in the record before applying the *Althen* test so that the special master could subsequently determine causation relative to the injury."). The Vaccine Act provides that a treating physician's diagnosis "shall not be binding on the special master or court," but that the special master should consider the "entire record and the course of the injury" when evaluating how much weight to afford a treating physician's diagnosis. 42 U.S.C. § 300aa-13(b)(1). In this case, Petitioner alleged that she suffered from PUK, uveitis, and herpes keratitis. She therefore must show by preponderant evidence that she suffers from each condition. *See Broekelschen*, 618 F.3d at 1349; *see also Lombardi*, 656 F.3d at 1353.

Petitioner has failed to show by preponderant evidence that she suffered from PUK. Although three of Petitioner's treaters initially diagnosed her with PUK, they all later ruled it out. Most notably, two of Petitioner's treating ophthalmologists altered their diagnoses in light of Petitioner's symptomatology and progression. Dr. Foote, who was the first to formally diagnose Petitioner with PUK, later agreed with Dr. Ostern that Petitioner suffered from herpetic keratouveitis that was exacerbated by her positive HLA-B27 status. Pet'r's Ex. 5 at 73–74 (citing Pet'r's Ex. 11 at 1). Dr. Di Pascuale, another treating ophthalmologist, concluded that Petitioner did not have PUK but rather HSV-related sclerokeratitis. Pet'r's Ex. 7 at 7–8, 29, 31. Dr. Smith, a rheumatologist, also altered her diagnosis and assessed Petitioner with Reiter's syndrome with herpes keratitis, noting specifically "Reiter's keratitis with herpes as the AG [aggravating] driver." Pet'r's Ex. 8 at 5–6, 11. Dr. Smith also proposed several other conditions to explain Petitioner's condition, including inflammatory eye disease, hypopyon uveitis, and Behcet's syndrome. *Id.* at 1, 7, 11. Additionally, upon establishing care with ophthalmologist Dr. Ramirez, he noted Petitioner's history of PUK but, after his own review, diagnosed her with severe vasculitis with associated keratitis. Pet'r's Ex. 6 at 1–4. It is therefore not likely that Petitioner's treaters believed she suffered from PUK.[68] In fact, Petitioner's own expert in ophthalmology opined that she never

[68] Petitioner's primary care physician Branch Craige made a note of Petitioner's self-reported history of PUK. Pet'r's Ex. 9 at 2. He also noted that Petitioner was being treated by Dr. Karen Smith for Reiter's syndrome. *Id.* His separate assessment of Petitioner documented "Reiter [sic] syndrome, HLA-B27 positive." *Id.* at 3. Therefore, his reference to Petitioner's history of PUK does not provide support for such a diagnosis.

suffered from PUK but rather "uveitis caused by the vaccine." *See* Pet'r's Ex. 19 at 2. Dr. Fraunfelder relied on Petitioner's symptom presentation and her response to initial treatment on November 12, 2012, to establish that her condition was consistent with uveitis instead of PUK. Notably, Petitioner seemed to abandon her claim as it relates to PUK and instead chose to proceed only with her uveitis and herpes keratitis claims. *See, e.g.*, Pet'r's Br. at 1, 17. Indeed, Petitioner's ensuing claim hinges on her not having PUK. Therefore, Petitioner has failed to show by preponderant evidence that she suffers from PUK and this condition will not be analyzed in relation to causation-in-fact.

Petitioner has presented preponderant evidence that she suffered from uveitis. Both Petitioner's and Respondent's experts agree that Petitioner exhibited "well-recognized" symptoms consistent with uveitis, including inflammation, pain, and redness of the eye. Pet'r's Ex. 19 at 2; Resp't's Ex. A; Tr. 18, 108. However, the experts disagree about when her uveitis manifested and the chain of cause and effect resulting in her uveitis. This discrepancy will be discussed with respect to *Althen* prongs two and three. However, for the purposes of determining diagnosis, Petitioner has shown by a preponderant standard that she suffers from uveitis.

Petitioner has also presented preponderant evidence that she suffered from a herpesvirus infection, which progressed to herpes keratitis. Neither expert disputes the fact that Petitioner suffered from either a primary or reactivated latent herpesvirus infection. Pet'r's Ex. 19 at 2; Resp't's Ex. A. Petitioner's expert opined that Petitioner's herpesvirus progressed to herpes keratitis.[69] While Respondent's expert did not explicitly admit that Petitioner suffered from herpes keratitis, he implied it in light of her HSV infection, and he did not deny that she has the condition. Indeed, the fact that several of Petitioner's treating physicians ultimately diagnosed her with herpes-related keratitis after ruling out other conditions, as described above, provides preponderant support for establishing such diagnosis. Additionally, two of Petitioner's treating ophthalmologists, Drs. Ostern and Ramirez, diagnosed her with keratitis with an infectious etiology, such as herpes, despite her cultures being negative. Pet'r's Ex. 11 at 1; Pet'r's Ex. 6 at 4. It is persuasive that, in support for his own theory, Respondent's expert opined that Petitioner's testing from August of 2013 and thereafter did not show signs of viruses, such as the herpesvirus, because "these samples had been obtained well after several rounds of therapy with multiple topical and systemic antibiotics and antivirals." Resp't's Ex. A at 4; *see also* Tr. 91:1–13. Respondent's reliance on the Tsatsos et al.,[70] article to show that the use of antivirals, such as Acyclovir, are used to prevent recurrent episodes of HSV is compelling evidence that Petitioner's steady treatment course with appropriate antivirals explains her negative cultures at the time of testing. *See* Resp't's Ex. I at 6. Therefore, Petitioner has shown by a preponderance of the evidence that she suffers from herpes keratitis.

### B. Experts

Although special masters have the discretion to be informed by past rulings and experiences, case-specific filings and testimony are the most helpful types of evidence, given the fact-specific nature of each decision. *See Doe v. Sec'y of Health & Hum. Servs.*, 76 Fed. Cl. 328, 338–39 (2007). To that end, experts are an essential piece of a petitioner's claim and Respondent's

[69] *See supra* note 5 (defining herpes keratitis as "a viral infection of the eye caused by HSV.").
[70] *See* Tsatsos, et al., *supra* note 65 at 1.

defense. Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen*, 618 F.3d at 1347 (citing *Lampe v. Sec'y of Health & Hum. Servs.*, 219 F.3d 1357, 1361 (Fed. Cir. 2000)).

This case ultimately turns not only on Petitioner's medical history, but also the persuasiveness of the written reports, supporting documentation, and expert testimony. I therefore must assess each expert's expertise in relation to the facts of Petitioner's case and assign weight accordingly. This assessment will inform my analysis pursuant to each prong of *Althen*.

I base this decision on entitlement, in part, on Dr. Bassiri's credentials and expertise in immunology and infectious diseases specifically, as compared to Dr. Fraunfelder's main focus in ophthalmology. While I in no way discount Dr. Fraunfelder's understanding and experience involving immunology, I must afford Dr. Bassiri's specialized knowledge in immunology and infectious diseases more weight. Notably, in relevant part, Dr. Bassiri received a Ph.D. in immunology from the University of Pennsylvania in 2002. Resp't's Ex. B at 1. Dr. Bassiri has been an attending physician in the Division of Infectious Disease, Department of Pediatrics at the Children's Hospital of Philadelphia for a decade. *Id.* He currently sees patients with immunodeficiencies, and studies T-cell function as part of his research for cancer immunotherapy. Tr. 65:10–14. He also frequently gives lectures regarding concepts of infectious diseases, such as herpesviruses and immunology. Tr. 66:5–6, 12–14.

Dr. Fraunfelder is an extremely qualified expert in his field. He has a history of providing useful testimony and persuasive explanations in cases before me, as well as other special masters in the Program. In this case however, his ultimate opinion was delivered with ambiguities, compared to the well-reasoned opinion of Respondent's expert. *See Broekelschen*, 618 F.3d at 1347 (citing *Lampe*, 219 F.3d at 1362) (finding that where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories."). Further, Dr. Bassiri's background and knowledge in immunology and infectious diseases is more applicable to this case than Dr. Fraunfelder's expertise in ophthalmology when considering the parties' arguments regarding the immunologic response involved in Petitioner's proposed mechanism and the infectious nature and immunological involvement of herpesviruses, such as HSV.

### C. *Althen* Prong One

Under the first prong of *Althen*, a petitioner must offer a scientific or medical theory that answers in the affirmative the question: "can the vaccine[] at issue cause the type of injury alleged?" *See Pafford v. Sec'y of Health & Hum. Servs.*, No. 01-0165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004), *mot. for rev. denied*, 64 Fed. Cl. 19 (2005), *aff'd*, 451 F.3d 1352 (Fed. Cir. 2006). To satisfy this prong, a petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen*, 35 F.3d at 548. Such a theory must only be "legally probable, not medically or scientifically certain." *Knudsen*, 35 F.3d at 548–49. Petitioners are not required to identify "specific biological mechanisms" to establish causation, nor are they required to present "epidemiologic studies, rechallenge[] the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities." *Capizzano,*

440 F.3d at 1325 (quoting *Althen*, 418 F.3d at 1280). Scientific and "objective confirmation" of the medical theory with additional medical documentation is unnecessary. *Althen*, 418 F.3d at 1278–81; *see also Moberly*, 592 F.3d at 1322. However, as the Federal Circuit has made clear, "simply identifying a 'plausible' theory of causation is insufficient for a petitioner to meet her burden of proof." *LaLonde v. Sec'y of Health & Hum. Servs.*, 746 F.3d 1334, 1339 (Fed. Cir. 2014) (citing *Moberly*, 592 F.3d at 1322). Rather, "[a] petitioner must provide a reputable medical or scientific explanation that pertains specifically to the petitioner's case." *Moberly*, 592 F.3d at 1322. In general, "the statutory standard of preponderance of the evidence requires a petitioner to demonstrate that the vaccine more likely than not caused the condition alleged." *LaLonde,* 746 F.3d at 1339.

Furthermore, establishing a sound and reliable medical theory connecting the vaccine to the injury often requires a petitioner to present expert testimony in support of her claim. *Lampe*, 219 F.3d at 1361. The Supreme Court's opinion in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), requires that courts determine the reliability of an expert opinion before it may be considered as evidence. "In short, the requirement that an expert's testimony pertain to 'scientific knowledge' establishes a standard of evidentiary reliability." *Id*. at 590 (citation omitted). Thus, for Vaccine Act claims, a "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly*, 592 F.3d at 1324. The *Daubert* factors are used in the *weighing* of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Hum. Servs.*, 94 Fed. Cl. 53, 66–67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted."). Nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder v. Sec'y of Health & Hum. Servs.*, 88 Fed. Cl. 706, 743 (2009) (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)).

**a. Uveitis**

Petitioner has failed to meet her burden under *Althen* prong one with respect to uveitis. Petitioner posited a scientific or medical theory explaining the flu vaccine's role in the development of uveitis through a Type IV hypersensitivity reaction and the notion of positive rechallenge. I will discuss each in turn.

**i. Type IV Hypersensitivity Reaction**

Petitioner relied on the Meng et al.[71] article to describe a Type IV hypersensitivity reaction. The authors emphasized the role of dendritic cells that "take up and process" antigens which are then represented on the surface of those cells with specific peptide – HLA complexes for T-cell recognition. Pet'r's Ex. 33, Tab B at 5. They explained that from there, the interaction between dendritic and T cells dictates the specificity of the reaction and location of the inflammatory response. *See id.* While Petitioner's reliance on the Meng et al. article aids my understanding of the mechanisms underlying a Type IV hypersensitivity response, the article does not advance Petitioner's case with respect to the flu vaccine and uveitis under *Althen* prong one. Petitioner's

[71] *See* Meng, et al., *supra* note 41 at 1.

main support for her biological mechanism is the Nussenblatt[72] animal model, which she contends shows that her proposed mechanism connecting the flu vaccine to uveitis has been tested and documented in the existing medical literature. *See* Pet'r's Ex. 33, Tab C. Further, Dr. Fraunfelder argues that this study proves that a systemically applied immunization can cause a localized inflammation, such as uveitis, via a Type IV hypersensitivity reaction. Tr. 38:1–3. However, Petitioner's reliance on this study is wholly misplaced. While the study discusses the role of Type IV hypersensitivity reactions in the development of uveitis, it fails to discuss vaccines in general, or the flu vaccine specifically. Instead, the rats in the study developed localized inflammation after being injected with a retinal S-antigen.[73] Pet'r's Ex. 33, Tab C at 2. The article therefore fails to show how a systemic flu vaccine can produce a localized Type IV hypersensitivity reaction.

Petitioner did not otherwise submit evidence supporting her theory that the flu vaccine can cause uveitis via a Type IV hypersensitivity reaction.[74] Instead, Petitioner conceded that the mechanisms underlying Type IV hypersensitivity reactions "are complex and not completely understood." Pet'r's Ex. 33 at 1. While Petitioner is not required to present objective confirmation or epidemiological studies to support her biological mechanism, she must do more than simply identify a "plausible" theory of causation. *Capizzano,* 440 F.3d at 1325 (quoting *Althen*, 418 F.3d at 1280); *see also LaLonde*, 746 F.3d at 1339 (citing *Moberly*, 592 F.3d at 1322). I therefore find that Petitioner has failed to show by preponderant evidence that the flu vaccine can cause uveitis via a Type IV hypersensitivity reaction.

Additionally, while prior decisions of special masters are not binding on my analysis, it is persuasive that Petitioner's proposed Type IV hypersensitivity reaction theory has previously been rejected in the Program. *See Yates v. Sec'y of Health & Hum. Servs.,* No. 14-560V, 2020 WL

[72] *See* Nussenblatt, *supra* note 40 at 1.

[73] A retinal S-antigen (S-ag) is not akin to a vaccine. Rather, it is "found in the photoreceptors of the eye, [and] is a potent autoantigen that is commonly involved in inflammatory eye disease leading to blindness[.]" *See* abstract of Suleyman, et al., *Idiotypic Expression of Antibodies to Retinal S-antigen in Experimental Autoimmune Uveoretinitis,* 62(4) IMMUNOL. 537–41 (1987).

[74] Petitioner's reliance on other articles showing a connection between the flu vaccine and uveitis is informative but inapplicable to *Althen* prong one, as the articles do not indicate that this phenomenon occurs because of a Type IV hypersensitivity reaction. For instance, Petitioner relied on the Benage et al. article to show that an association exists between the flu vaccine and uveitis, as twenty-eight instances were reported over a thirty-year period. Pet'r's Ex. 19, Tab A. However, the article does not describe a causal connection between the flu vaccine and uveitis, nor does it elaborate on the mechanism by which this occurs. *See id.* Petitioner relied on the article by London et al., which used the Naranjo criteria in place of a clinical trial, to determine that the flu vaccine has a "probable" causal association with uveitis. Pet'r's Ex. 45 at 4, 13. The authors determined this score signified more than a mere possibility of occurrence, but still less than definite probability. *Id.* It does not identify a biological mechanism. *Id.* Similarly, Petitioner also relied on the article by Suhler et al. to argue that all vaccinations can cause a Type IV hypersensitivity reaction. Pet'r's Ex. 19, Tab D at 4. However, Petitioner conceded that the Suhler et al. article is distinguishable because the article talks about the Hepatitis B vaccine, not the flu vaccine, and the authors allege a Type III hypersensitivity reaction as the mechanism, not a Type IV. Tr. 53:23–25, 54:1–17 (citing Pet'r's Ex. 19, Tab D). The authors also fail to elaborate on the mechanics of a "delayed-type hypersensitivity reaction[,]" merely stating that it is one possible mechanism for the development of uveitis. Pet'r's Ex. 19, Tab D at 4. As Respondent's expert correctly maintained, the distinctions between the types of hypersensitivity reaction are not "merely semantics" and instead, implicate different cell responses. Therefore, I must afford such articles little to no weight.

2313691 (Fed. Cl. Spec. Mstr. Apr. 16, 2020), *mot. for rev. denied,* 150 Fed. Cl. 575 (2020) (finding that Petitioner failed to explain how a T-cell mediated Type IV hypersensitivity immune response to a Menactra vaccine can cause lymphocytic myocarditis, as there is a distinction between lymphocytic myocarditis being viral and eosinophilic myocarditis being a hypersensitivity reaction.); *see also Forrest v. Sec'y of Health & Hum. Servs.,* No. 10-032V, 2017 WL 4053241 (Fed. Cl. Spec. Mstr. Aug. 10, 2017) (rejecting Petitioner's argument that four-month infant vaccinations, including Hep. B, inactivated polio, diphtheria-tetanus-acellular pertussis, haemophilus influenza, and pneumococcal conjugate vaccines, could cause a Type IV hypersensitivity reaction resulting in sudden infant death syndrome ("SIDS"). The special master based this decision, in part, on Petitioner's failure to provide evidence in favor of a Type IV response other than the time between vaccination and injury. The special master acknowledged that the fever the infant experienced post vaccination was not a Type IV response but a humoral or antibody sensitivity.). While these cases are not completely analogous to Petitioner's case in terms of vaccine or injury, the special masters' reasoning for rejecting the proposed Type IV hypersensitivity reaction is informative.

**ii. Positive Rechallenge**

Petitioner has also failed to provide preponderant evidence establishing that the flu vaccine can cause uveitis via a positive rechallenge. While Dr. Fraunfelder's testimony explaining the concept of positive rechallenge is useful, Petitioner did not otherwise present evidence supporting her claim as it relates to this biological mechanism and uveitis. Dr. Fraunfelder testified that a positive rechallenge occurs when an individual receives a vaccine more than once and experiences a negative reaction following each subsequent receipt of the vaccine, as the body has seen that specific antigen before and reacts the same way. *See* Tr. 25–26. Even though Petitioner is not required to provide specifics of the biological mechanism or provide epidemiological studies that explain her disease pathology, to the extent that she does, they must make sense. Instead, Petitioner's submitted medical literature is inconsistent with her claim, and her reliance on the Suhler et al.[75] article is detrimental to her case. The authors of the article, including Petitioner's own expert, studied the Hep. B vaccine and the development of recurrent uveitis. Pet'r's Ex. 19, Tab D. The authors found that one patient in the study had recurrent uveitis after the second and third doses of the Hep. B vaccine. *Id.* at 1. Another patient in the study developed uveitis after the first dose of a Hep. B vaccine and again after the second. *Id.* This article is not completely analogous to Petitioner's case because it fails to discuss the flu vaccine. It also fails to support Petitioner's proposed biological mechanism of a positive rechallenge, as a patient in the study developed uveitis after the first exposure to the Hep. B vaccine. *See id.* As such, this article does not provide preponderant evidence to support Petitioner's claim regarding the flu vaccine causing uveitis via a positive rechallenge.

Petitioner also relies on the Hassman et al.[76] article to argue that a flu vaccine can cause severe inflammation in the central nervous system and recurrent uveitis through a positive rechallenge. Pet'r's Ex. 44 at 1. However, this article is inapplicable to Petitioner's claim as it relates to uveitis. The authors of the article found that the flu vaccine can play a role in the development of severe inflammation of the central nervous system, but only because the flu

[75] *See* Fraunfelder & Suhler, et al., *supra* note 38 at 1.
[76] *See* Hassman, et al., *supra* note 42 at 1.

vaccine can cause activation of *HSV*, not uveitis directly. *See id.* In fact, the article fails to mention uveitis altogether, and instead discusses retinitis.[77] While such conditions may be medically comparable because they both involve inflammation of the eye, the article fails to advance Petitioner's case pursuant to *Althen* prong one. Further, Petitioner's expert testified regarding an article by Knopf et al. as support for the notion of positive rechallenge based on its title, "Recurrent Uveitis After Influenza Vaccination." *See* Tr. 28:16–17. However, Dr. Fraunfelder did not rely on this article in any of his written reports. Petitioner did not file the full article, or even an abstract, for consideration. Instead, it was merely cited in another exhibit and briefly mentioned for the first time during his testimony. *See* Tr. 28:11–22; *see also* Pet'r's Ex. 19, Tab B. I therefore do not consider this article as support for Petitioner's claim. Petitioner has failed to show by preponderant evidence how the flu vaccine can cause uveitis via a positive rechallenge.

**b. Herpesvirus and Herpes Keratitis**

Petitioner argues that the flu vaccine causes an altered immune system via a Type IV hypersensitivity reaction, which creates a susceptibility to HSV, and herpes keratitis can develop. Petitioner does not, however, present preponderant evidence that a Type IV hypersensitivity reaction can lead to herpes keratitis. While Petitioner does not explicitly argue that the flu vaccine triggers HSV reactivation via a positive rechallenge, the record as a whole, including Petitioner's submitted medical literature and testimony from both experts, provides evidence that the flu vaccine can cause HSV reactivation and eventual herpes keratitis via a positive rechallenge. I find Petitioner has met her burden under *Althen* prong one with respect to the flu vaccine's role in the development of HSV reactivation and subsequent herpes keratitis via the notion of a positive rechallenge.

**i. Type IV Hypersensitivity Reaction**

Petitioner alleges that because the flu vaccine can act as an immunological trigger resulting in an altered immune status and uveitis, said vaccine also creates a susceptibility to HSV and the development of herpes keratitis. Dr. Fraunfelder argues that this occurs because a Type IV hypersensitivity reaction alters the immune system and "[w]hen a person develops an eye disease . . . they are susceptible to opportunistic infections from viruses that are dormant within [the body,]" such as HSV. Pet'r's Ex. 19 at 2; Tr. 43:21–25. Respondent's expert's testimony regarding the expected immune response caused by a Type IV hypersensitivity reaction directly contradicts Dr. Fraunfelder's argument. Indeed, Dr. Bassiri's expertise in immunology is evident during his rebuttal of Dr. Fraunfelder's argument. Dr. Bassiri explained that a Type IV hypersensitivity reaction would not lead to an altered immune system, because a Type IV reaction produces a localized inflammatory response that dissipates, similar to that of a PPD test or poison ivy. Dr. Bassiri continued that this type of reaction is not systemic and manifests as localized itchiness, not a fever. Dr. Bassiri then compared the types of hypersensitivity reactions and explained that a "[T]ype IV hypersensitivity is rarely associated with fever – especially when the inoculum size of the antigen (e.g., that in influenza vaccines) is small." Resp't's Ex. M at 2; Tr. 73:1–6. He admitted that a fever could occur in a Type IV hypersensitivity reaction "if you were to give somebody who

[77] Retinitis is "inflammation of the retina, marked by impairment of sight, abnormalities of vision, edema, and exudation into the retina, and occasionally by hemorrhages into the retina. The term is sometimes used more loosely to denote also noninflammatory disorders of the retina." *Dorland's* at 1633.

has a prior sensitization a large amount of that antigen, you would have a relatively large or robust immune response[,] . . . the end result of which could be fever." Tr. 107:2–8. It therefore stands to reason that the typical immunologic response triggered by a Type IV hypersensitivity reaction would not rise to the level of altering or weakening the immune system when it generally fails to produce any systemic response.

Turning to the herpesvirus specifically, which is responsible for the development of herpes keratitis,[78] Dr. Bassiri testified that the manifestation of a primary herpesvirus infection would not presumably implicate altered immunity "in the pathogenesis of this infection[]" because primary HSV infections commonly occur without a trigger in immunocompetent individuals. Dr. Bassiri explained that reactivation of HSV infections can occur if a patient is immunosuppressed because the patient is more prone to developing latent viruses. He also noted reactivation can occur in healthy patients, wherein the immune system is not implicated. Based on this, he reasonably concluded that he did not see an immunological association with T-cell activation and reactivation of HSV, a requisite for the development of a Type IV hypersensitivity. Overall, Petitioner's proposal that a Type IV hypersensitivity reaction weakens the immune system to the point that "opportunistic" infections like HSV surface, is not sufficiently supported. *See* Tr. 42:21–23. Therefore, Petitioner has failed to show how a Type IV hypersensitivity reaction can result in the manifestation of HSV and the development of herpes keratitis.

**ii. Positive Rechallenge**

Even though Dr. Bassiri's testimony refutes Petitioner's claim with respect to the flu vaccine causing HSV and herpes keratitis via a Type IV hypersensitivity reaction, the same is not true regarding the notion of positive rechallenge. Indeed, Dr. Bassiri conceded that it is rare but "possible" that a vaccine could reactivate a latent HSV infection, which is a "known cause" of herpes keratitis.[79] *See* Tr. 110:18–22; Resp't's Ex. A at 3–4. This phenomenon is supported by Petitioner's reliance on the Hassman et al.[80] article, which noted that the flu vaccine triggered the reactivation of a latent HSV infection in 13 out of 38 million doses over ten years. Pet'r's Ex. 44 at 5. While this article did not advance Petitioner's case with respect to a positive rechallenge and uveitis, it does provide support for her claim that the flu vaccine can trigger the reactivation of a HSV infection via a positive rechallenge. Indeed, the authors determined that "disruptions" in the immune system, such as vaccines, can activate the virus. *Id.* at 1. To support their conclusion, the authors noted a study wherein the patient had "three consecutive yearly [HSV] episodes (encephalitis, seizure, and retinitis), each within days of his influenza vaccination." *Id.* The authors found that, through a positive rechallenge, a flu vaccine can cause severe inflammation in the central nervous system, which can lead to infection with HSV and herpes encephalitis. *Id.*; Tr. 45:4–21. However, it is important to note that the authors conceded that "[a] subtle immunological deficiency in [their] patient may have lowered the threshold for clinically significant HSV reactivation in the [central nervous system]." Pet'r's Ex. 44 at 5. Nonetheless, this study supports Petitioner's claim related to positive rechallenge, as the patient in the study experienced a re-occurrence of HSV-related symptoms and ailments upon re-administration of subsequent flu vaccines.

[78] *See supra* note 5 (defining herpes keratitis as "a viral infection of the eye caused by HSV.").
[79] *See id.*
[80] *See* Hassman, et al., *supra* note 42 at 1.

While the Hassman et al. study shows that this occurrence is uncommon (13 out of 38 million doses over ten years), I do not find persuasive Respondent's argument that because we have not seen this occur often, it could not occur. Simply because HSV does not require a trigger to manifest does not mean that a flu vaccine could not be the trigger, especially if the individual has had negative reactions from repeated exposure to the same vaccine. I do not find Dr. Bassiri's arguments regarding the rarity of this occurrence to be equivalent to an explanation of the improbability of this type of occurrence. In fact, Petitioner's expert also conceded that this occurrence is rare, and he has not seen it throughout the course of his career in ophthalmology. However, such concessions do not weaken Petitioner's argument under *Althen* prong one. Indeed, by the nature of the Program, a petitioner's claims often arise out of the rarest and most unique of circumstances. As absolute certainty is not the standard in the Program, I find that Petitioner has presented preponderant evidence establishing that a flu vaccine can trigger HSV through a positive rechallenge. *See Althen*, 418 F.3d at 1278–81; *see also Moberly*, 592 F.3d at 1322 (finding scientific and "objective confirmation" of the medical theory with additional medical documentation is unnecessary.). Accordingly, I find Petitioner has satisfied prong one of *Althen* with respect to HSV and herpes keratitis.

### D. *Althen* Prong Two

Under the second prong of *Althen*, a petitioner must prove that the vaccine actually did cause the alleged injury in a particular case. *See Pafford*, 2004 WL 1717359, at *4; *Althen*, 418 F.3d at 1279. The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Capizzano*, 440 F.3d at 1326; *Grant v. Sec'y of Health & Hum. Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). A petitioner does not meet this obligation by showing only a temporal association between the vaccination and the injury; instead, the petitioner "must explain *how* and *why* the injury occurred." *Pafford*, 2004 WL 1717359, at *4 (emphasis in original). The special master in *Pafford* noted petitioners "must prove [] both that her vaccinations were a substantial factor in causing the illness . . . and that the harm would not have occurred in the absence of the vaccination." 2004 WL 1717359, at *4 (citing *Shyface*, 165 F.3d at 1352). A reputable medical or scientific explanation must support this logical sequence of cause and effect. *Hodges v. Sec'y of Health & Hum. Servs.,* 9 F.3d 958, 961 (Fed Cir. 1993) (citation omitted). Nevertheless, "[r]equiring epidemiologic studies . . . or general acceptance in the scientific or medical communities . . . impermissibly raises a claimant's burden under the Vaccine Act and hinders the system created by Congress . . . ." *Capizzano*, 440 F.3d at 1325–26. "[C]lose calls regarding causation are resolved in favor of injured claimants." *Althen*, 418 F.3d at 1280.

In Program cases, contemporaneous medical records and the opinions of treating physicians are favored. *Capizzano*, 440 F.3d at 1326 (citing *Althen*, 418 F.3d at 1280). Indeed, when reviewing the record, a special master must consider the opinions of treating physicians. *Capizzano*, 440 F.3d at 1326. This is because "treating physicians are likely to be in the best position to determine whether 'a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" *Id.* In addition, "[m]edical records, in general, warrant consideration as trustworthy evidence. The records contain information supplied to or by health professionals to facilitate diagnosis and treatment of medical conditions. With proper treatment hanging in the balance, accuracy has an extra premium. These records are also generally

contemporaneous to the medical events." *Cucuras v. Sec'y of Health & Hum. Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993). While a special master must consider these opinions and records, they are not "binding on the special master or court." 42 U.S.C. § 300aa-13(b)(1). Rather, when "evaluating the weight to be afforded to any such . . . [evidence], the special master . . . shall consider the entire record . . . ." *Id.* The record often includes "evidence of possible sources of injury" that can show alternate causes for the alleged vaccine-related injury. *See Stone v. Sec'y of Health & Hum. Servs.,* 676 F.3d 1373, 1379 (Fed. Cir. 2012).

I have considered the notations[81] from Petitioner's treaters ascribing causation to the flu vaccine, but I must weigh such records against Petitioner's treaters that considered both her flu vaccine and HSV status, and alternatively ascribed causation to the latter. *See supra* Section V.A.; *see also* 42 U.S.C. § 300aa-13(b)(1) (finding statements of treating physicians are not binding on special masters and the special master shall consider the entire record); *Capizzano*, 440 F.3d at 1326 (citing *Althen*, 418 F.3d at 1280); *Pafford*, 2004 WL 1717359, at *4; *Stone,* 676 F.3d at 1379. Additionally, such notations were made more than two years after Petitioner's November 3, 2012 flu vaccine, and Petitioner has failed to present preponderant evidence that such notations refer to the flu vaccine at issue. *See* Pet'r's Ex. 35 at 2; Pet'r's Ex. 30 at 1 (noting that Petitioner experienced reactions to a flu vaccine in 2014 and a TB test in 2016). When considering the record as a whole, I must afford Petitioner's treaters' notations ascribing causation to the flu vaccine less weight. For the reasons discussed herein, Petitioner has failed to establish that it is more likely than not that the flu vaccine administered on November 3, 2012, caused her to develop uveitis and herpes keratitis. As such, Petitioner has failed to satisfy prong two of *Althen. See Hodges,* 9 F.3d at 961 (noting that "[a] reputable medical or scientific explanation must support this logical sequence of cause and effect.").

**a. Uveitis**

Petitioner has failed to provide preponderant evidence that her November 3, 2012 flu vaccine caused her uveitis via her proposed biological mechanisms pursuant to *Althen* prong two.

**i. Type IV Hypersensitivity Reaction**

Petitioner argued, based solely on the time between vaccination and onset of symptoms, that she suffered a Type IV hypersensitivity reaction resulting in uveitis. Her expert was otherwise unable to identify any signs or symptoms that distinguished her alleged vaccine-caused uveitis via

[81] On November 6, 2014, Dr. Karen Smith indicated that Petitioner "[i]n reviewing her records[, ] noted the eye inflammatory disease came on immediately after the flu shot." Pet'r's Ex. 8 at 1. Dr. Smith wrote that "[i]t is immunologically possible that this could be the trigger." *Id.* On April 18, 2016, Dr. Lawal, a cardiologist Petitioner saw for heart murmurs, noted that she had an autoimmune reaction in her right eye after a flu shot two years ago. Pet'r's Ex. 35 at 2. Dr. Smith noted on November 4, 2016, that Petitioner was given a TB test, had an "enormous" reaction, and experienced a flare in her eye symptoms ever since. Pet'r's Ex. 30 at 1. Dr. Smith then went so far as to warn Petitioner "to avoid all things that stimulate dendritic cells which is vaccines . . . as it activates her eye disease[.]" *Id.* Petitioner's treater in Norway, Dr. Ostern, also noted that Petitioner "seems to react strongly to vaccines . . . [t]his is assumed to secondarily set off herpes keratitis." Pet'r's Ex. 38 at 2A. Such notations do not provide preponderant support for Petitioner's claim that her November 3, 2012 flu vaccine caused her uveitis and related injuries.

a Type IV hypersensitivity reaction from uveitis that is not caused by a vaccine. Respondent's expert, however, was able to describe signs and symptoms that would signify Petitioner *did not* experience a Type IV hypersensitivity reaction caused by the flu vaccine. Dr. Bassiri's reliance on the record to support his position is persuasive.

Dr. Bassiri credibly and consistently explained that a Type IV hypersensitivity reaction would not manifest as a fever, stye, or nasal tenderness, as it did in Petitioner's case. *See* Resp't's Ex. A at 3; Tr. 74:6–10. While Dr. Bassiri admitted that a Type IV hypersensitivity reaction could result in fever if you were to give someone who has a prior sensitization a large amount of that antigen, such occurrence is inapplicable to the facts of Petitioner's case. Dr. Bassiri recounted Petitioner's vaccination record and noted that she "at least checked a box" that she had never had a negative reaction to previous flu vaccines. *See, e.g.*, Pet'r's Ex. 1 at 1. Petitioner also failed to provide evidence showing that she received a high-dose flu vaccine with an amount of an antigen large enough to induce a Type IV hypersensitivity response. The record does not provide preponderant evidence that she had a sensitization to the components of the flu vaccine; therefore, she has not established by preponderant evidence that she experienced a systemic response to her flu vaccine that altered her immune system via a Type IV reaction. Petitioner has failed to show that it is more likely than not that her November 3, 2012 flu vaccine caused her uveitis via a Type IV hypersensitivity reaction.

In this case, Respondent does not have a burden to prove Petitioner's injuries were caused by something other than her flu vaccine because Petitioner is unable to establish a prima facie case of vaccine-caused uveitis pursuant to *Althen* prong two. *See LaLonde,* 746 F.3d at 1340. However, Respondent has presented numerous arguments related to alternative causes, and I will consider those applicable to his argument that Petitioner has not met her burden showing that her flu vaccine was the cause of her uveitis via the proposed biological mechanism. *See Stone,* 676 F.3d at 1379 (finding that the record often includes "evidence of possible sources of injury" that can show alternate causes for the alleged vaccine-related injury.).

Dr. Bassiri referenced Petitioner's symptoms noted several days post vaccination, including her fever and "mild cold" symptoms, such as nasal inflammation and tenderness, to support his assertion that Petitioner did not experience a Type IV hypersensitivity reaction. Instead, he relied on these same symptoms to opine that Petitioner experienced either a primary or reactivated herpesvirus, leading to her herpes keratitis and uveitis. Resp't's Ex. A at 4 (citing Pet'r's Ex. 2 at 1).

Respondent's argument, that in both the primary and reactivation of herpesviruses, "one can see systemic signs of [] an illness, such as fever[]" and other cold symptoms, is well-supported by the medical literature. Tr. 74:20–25, 75:4–5, 76:1–5. The articles by Darougar & Wishart et al.[82] provide that such cold symptoms are common findings accompanying either a primary or reactivation of the herpesvirus. Their findings are significant in that they found that in primary herpesvirus ocular infections, upper respiratory tract or "cold" symptoms, such as nasal inflammation and tenderness, are observed in 35% of patients, with fever in 31% of cases. Resp't's Ex. E at 1. Their comparison to reactivated herpesvirus ocular infections is notable in that they found such upper respiratory tract or cold symptoms, including fever, occurs in 48% of cases.

[82] *See* S. Darougar & M.S. Wishart, et al., *supra* note 63.

Resp't's Ex. L at 2. Even more persuasive, is that the authors also found that "15 and 23% of patients with primary or reactivation herpesvirus ocular infections displayed chronic blepharitis (inflammation of the eyelid margin)." Resp't's Ex. A at 4. Dr. Bassiri's explanation that blepharitis is a symptom of herpesviruses, and presents as inflammation in the eyelid, supports his opinion that Dr. Alvarez misdiagnosed Petitioner with a stye on November 12, 2012. Petitioner's symptoms of fever and mild cold symptoms, including nasal tenderness and inflammation plus blepharitis three days post vaccination, provide strong evidence that she was suffering the onset of her herpesvirus infection at that time, rather than a Type IV hypersensitivity reaction caused by the flu vaccine.

**ii. Positive Rechallenge**

Petitioner's assertion that a positive rechallenge caused her uveitis is greatly hindered by Dr. Fraunfelder's admission that he did not know if Petitioner had ever received a prior flu vaccine, or if she had a negative reaction to prior flu vaccines. Petitioner did not offer that information, either through testimony or affidavit.[83] Yet, as noted, Dr. Bassiri recounted Petitioner's vaccination record and indicated that Petitioner had received the flu vaccine before and had "at least checked a box" that she had never had a negative reaction to previous flu vaccines. *See, e.g.*, Pet'r's Ex. 1 at 1. Dr. Bassiri's reliance on the record to support his position is determinative. Dr. Fraunfelder's omission regarding Petitioner's exposure and reaction to prior flu vaccines prevents Petitioner from establishing a logical chain of cause and effect for a "positive rechallenge" as it pertains to her uveitis.

While Petitioner's reliance on the Hassman et al.[84] article was informative to *Althen* prong one, Respondent has successfully negated its effectiveness as it relates to Petitioner's case under *Althen* prong two. The authors of the article discussed an immunodeficient patient who experienced reactions to repeated vaccinations. Pet'r's Ex. 44 at 1. Respondent effectively distinguished this case from Petitioner's by noting that the record does not contain evidence that she had a pre-existing immune defect[85] or experienced negative reactions to "repeated vaccinations[,]" as previously discussed. Tr. 79:18–20, 80:7–9. Petitioner's reliance on the London

[83] At the conclusion of the hearing, I noted that Petitioner exercised her right not to testify. Therefore, I do not have "the benefit of the doubt on something that I don't know." Tr. 136:7–8. I indicated that even if she were to submit written affidavits, they would not "have nearly the same weight as being questioned in real time[.]" Tr. 136:9–13. I continued that Petitioner would "have the benefit of knowing exactly what answers are the right answers." Tr. 136:13–14. I stressed that I was not suggesting that Petitioner would "intentionally deceive" the Court, but I acknowledged that "there is a tendency, just human nature, to remember things in such a way that fit in with your . . . perspective of what happened." Tr. 136:15–18. Petitioner ultimately did not request, nor did I order her to, submit affidavits on unresolved facts.

[84] *See* Hassman, et al., *supra* note 42 at 1.

[85] Respondent's expert addressed Petitioner's family history and genetic susceptibility for developing autoimmune diseases, such as uveitis, following viral infections like herpesviruses. He explained that the fact that Petitioner has a sister "with possible rheumatoid arthritis" and a son with "possible ankylosing spondylitis" suggests "a relatively strong predisposition to autoimmune diseases." Resp't's Ex. A at 5. He also testified that a positive HLA-B27 haplotype, present in Petitioner, may result in a predisposition to a variety of autoimmune phenomenon, including uveitis. Tr. 85:1–3. While Respondent noted potential genetic susceptibilities and predispositions to autoimmune diseases, the record fails to provide preponderant evidence that Petitioner, in fact, suffers from an immune *defect*.

et al.[86] article is also inapplicable to her case under *Althen* prong two. The Naranjo criteria, as applied to Petitioner, do not support her claim that the flu vaccine caused her uveitis and ensuing injuries. While the authors of the London et al. article found that a "probable" association exists between the flu vaccine and uveitis in general, Respondent's application of the Naranjo criteria to the facts of Petitioner's case casts doubt on her theory that she experienced her injuries via her proposed biological mechanism. Indeed, when Respondent's expert applied the Naranjo criteria to Petitioner's case, he was able to consider her lack of negative reactions to prior flu vaccines and the potential for alternate causes that could explain her condition, which are "much more commonly accepted" as causes of both uveitis and herpes keratitis. *See* Tr. 81:23–25. Therefore, Petitioner has failed to show by a preponderant standard that her November 3, 2012 flu vaccine caused her uveitis via a positive rechallenge.

**b. Herpesvirus and Herpes Keratitis**

Petitioner has also failed to provide preponderant evidence that her November 3, 2012 flu vaccine triggered her herpesvirus and subsequent herpes keratitis via her proposed biological mechanisms pursuant to *Althen* prong two.

**i. Type IV Hypersensitivity Reaction**

Petitioner's argument that the flu vaccine acts as an immunological trigger, weakening the immune system via a Type IV hypersensitivity reaction and leading to HSV and herpes keratitis is not supported by the facts of her case. Indeed, Dr. Bassiri credibly explained that a Type IV hypersensitivity reaction would not alter the immune system. This is because a Type IV reaction produces a localized inflammatory response, such as itchiness. His testimony that a Type IV hypersensitivity reaction would not impact the immune system enough to produce a basic systemic response, such as a fever, is persuasive. Petitioner developed a fever three days post vaccination, which, as previously discussed, is more indicative of an HSV infection, rather than a Type IV hypersensitivity reaction. This conclusion is supported by the fact that Dr. Bassiri also testified that a Type IV hypersensitivity response could result in a fever, but only if you were to give someone with a prior sensitization a large amount of that antigen. *See* Resp't's Ex. M at 2; *see also* Tr. 73:1–6, 107:2–8. Petitioner, however, has failed to present preponderant evidence showing that she had a prior sensitization to flu vaccines. Her record affirmatively notes a lack of negative reactions in the past, and it does not reflect that she received a high-dose flu vaccine containing a large enough antigen to produce a fever via a Type IV hypersensitivity reaction. Petitioner has therefore failed to establish that her November 3, 2012 flu vaccine altered her immune system creating a susceptibility to HSV and subsequent herpes keratitis through a Type IV hypersensitivity reaction.

**ii. Positive Rechallenge**

As discussed, Petitioner cannot establish by preponderant evidence that the flu vaccine at issue caused a positive rechallenge, triggering the activation of her HSV. While the Hassman et al.[87] article described cases wherein a patient experienced three HSV-type illnesses following

[86] *See* London, et al., *supra* note 36 at 1.
[87] *See* Hassman, et al., *supra* note 42 at 1.

receipt of each yearly flu vaccine, Petitioner's record does not show that she had negative reactions to prior flu vaccines. Therefore, Petitioner cannot establish that her November 3, 2012 flu vaccine caused her HSV and herpes keratitis via a positive rechallenge.

### E. *Althen* Prong Three

Under the third prong of *Althen*, a petitioner must show that the timing of the injury fits with the causal theory. *See Althen*, 418 F.3d at 1278. For example, if a petitioner's theory involves a process that takes several days to develop after vaccination, an injury that occurred within a day of vaccination would not be temporally consistent with that theory. Conversely, if the theory is one that anticipates a rapid development of a reaction post vaccination, the development of the alleged injury weeks or months post vaccination would not be consistent with that theory. *See de Bazan*, 539 F.3d at 1352. Causation-in-fact cannot be inferred from temporal proximity alone. *See Grant,* 956 F.2d at 1148; *Thibaudeau v. Sec'y of Health & Hum. Servs.*, 24 Cl. Ct. 400, 403–04 (1991); *see also Hasler v. U.S.*, 718 F.2d 202, 205 (6th Cir. 1983) ("[w]ithout more, [a] proximate temporal relationship will not support a finding of causation.").

Petitioner has failed to meet her burden with respect to *Althen* prong three. She argues that the eye pain and redness she experienced three- to- four- days post vaccination was the onset of her vaccine-caused uveitis via a Type IV hypersensitivity reaction. Petitioner admitted that her medical records from November 12, 2012, nine days post vaccination, do not contain a diagnosis of uveitis, but rather that of a stye and conjunctivitis. *See, e.g.*, Pet'r's Ex. 2 at 1. It is persuasive that Petitioner's expert could not say unequivocally that Petitioner had uveitis during the time of her November 12, 2012 appointment. At best, he opined that she "probably had uveitis then[.]" *See* Tr. 18, 53. Petitioner's medical records do not reflect symptoms consistent with uveitis until January 7, 2013, approximately two months post vaccination. *See, e.g.*, Pet'r's Ex. 5 at 2; *see also* Pet'r's Ex. 19 at 1. Respondent's expert agreed that Petitioner experienced symptoms of uveitis, such as pain and redness, on January 7, 2013. Resp't's Ex. A at 3; Tr. 108:6–13. The presence of Petitioner's uveitis at that time is consistent with Petitioner's expert's concession that on January 7, 2013, Dr. Foote noticed additional symptoms consistent with uveitis, such as marked inflammation and keratic precipitates, that were not noted during Petitioner's November 12, 2012 visit. *See* Pet'r's Ex. 19 at 1.

While Respondent's expert admitted that Petitioner's medical records reflect that she was experiencing symptoms "consistent with uveitis," namely pain and redness, during her November 12, 2012 visit, his alternative explanation for the presence of those symptoms is compelling. *See* Tr. 108:6–16 (citing Pet'r's Ex. 2 at 1). It is informative that Respondent's expert noted that Petitioner experienced the onset of eye pain and redness "contemporaneous with her fever" beginning three- to- four days post vaccination. Tr. 108:17–21 (citing Pet'r's Ex. 16 at 1). He credibly explained, consistent with the medical literature,[88] that the pain and redness Petitioner experienced at this time contemporaneously with her fever, is actually evidence of a herpesvirus infection manifesting with blepharitis and cold symptoms instead of uveitis. Resp't's Ex. E at 1; Resp't's Ex. L at 2; Tr. 75:17–22. Petitioner has failed to establish by preponderant evidence that she experienced the onset of her uveitis beginning three- to- four days post vaccination or before November 12, 2012. She has presented preponderant evidence that she was suffering from uveitis

[88] *See* S. Darougar & M.S. Wishart, et al., *supra* note 63.

on January 7, 2013, but it is otherwise unclear when Petitioner's uveitis began. For purposes of evaluating Petitioner's claim under *Althen* prong three, I will assume *arguendo* that the onset of her uveitis was no earlier than January 7, 2013.

The timing of onset of Petitioner's uveitis does not support her theory of causation by means of a Type IV hypersensitivity reaction. *See de Bazan,* 539 F.3d at 1352. Respondent's opinion that a Type IV hypersensitivity reaction typically manifests within 24–48 hours of the vaccine, and peaks within 72–96 hours, is well-supported by the medical literature. In fact, the Chung[89] article documented the same onset interval for a Type IV hypersensitivity reaction. Pet'r's Ex. 33, Tab A at 2; Resp't's Ex. D at 2. Respondent's expert's evidence regarding how Type IV reactions "dissipate" and do not prolong for two or three weeks is persuasive. Tr. 73:14–16. Indeed, Dr. Bassiri's proffered examples of common Type IV hypersensitivity reactions, including PPD tests for tuberculosis, inform my decision. PPD tests are routinely read within 24–48 hours of injection because it is accepted that an inflammatory response will manifest during this time period, if applicable. Petitioner has therefore presented preponderant evidence that Type IV hypersensitivity reactions manifest within one- to- two days and peak at day three- to- four.

Petitioner did not provide preponderant evidence that her symptoms were consistent with uveitis until approximately two months post vaccination. The onset of Petitioner's injuries is therefore well outside the accepted timeframe for a Type IV hypersensitivity reaction to occur. It is convincing that Petitioner's expert could not support his opinion that Petitioner experienced a Type IV hypersensitivity reaction based on more than a temporal association. *See Grant,* 956 F.2d at 1148. In fact, after repeated questioning, Dr. Fraunfelder conceded that the only reason he opined that she experienced a Type IV hypersensitivity reaction in response to the flu vaccine was because of the time between vaccination and the onset of her symptoms. Tr. 61:19–25, 62:1–15. That is not the standard in the Program. *Grant,* 956 F.2d at 1148.

It is also compelling that neither expert discussed the onset time of a positive rechallenge. While the authors of the Hassman et al.[90] article found that the patient in the study experienced HSV flares "within days" of his yearly flu vaccines, without more, I am unable to find by a preponderant standard that Petitioner experienced the onset of her HSV symptoms consistent with the timeframe for a positive rechallenge to occur.

I find that Petitioner has failed to present preponderant evidence to establish that the onset of her uveitis occurred in a timeframe consistent with her proposed theory of causation. Therefore, she has failed to satisfy her burden under *Althen* prong three.

## VI. Conclusion

Petitioner has failed to establish by preponderant evidence that the flu vaccine she received on November 3, 2012, was the cause-in-fact of her uveitis and herpes keratitis. Therefore, the

[89] *See* Chung, *supra* note 39.
[90] *See* Hassman, et al., *supra* note 42 at 1.

evidence Petitioner presented has not demonstrated entitlement to compensation. Accordingly, this case is hereby **DISMISSED.**[91]

**IT IS SO ORDERED.**

s/Herbrina D. Sanders
Herbrina D. Sanders
Special Master

[91] Pursuant to Vaccine Rule 11(a), entry of judgment is expedited by the parties' joint filing of a notice renouncing the right to seek review.